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14. ABSTRACT The objective of this proposed study is to systematically define the clinical and logistical issues surrounding traditional open vascular surgery and catheter-based hemorrhage control. The hypothesis is that minimally invasive, device-driven and expert-led NCTH control techniques improve survival compared to traditional open vascular surgery. This project will achieve the following aims: 1) Determine current practice patterns for the treatment of patients with NCTH among 4 clinical sites using a retrospective study design (Phase 1a); 2) Conduct a 2-day Delphi Panel meeting of military and civilian experts to gain consensus regarding anatomic, technology, credentialing, competency, and training issues for catheter-based hemorrhage control (Phase 1b); 3) Conduct a prospective 4-site observational study to test the hypothesis that less-invasive device-driven and expert-led hemorrhage control techniques are associated with improved survival in NCTH patients and strengthen the evidence base to inform future development of catheters, devices, and training required for surgeons for catheter-based hemorrhage control (Phase 2). Patients undergoing endovascular intervention for NCTH experience longer time to intervention and definitive hemorrhage control. Given the narrow injury pattern, consideration should be given to increased endovascular training for trauma surgeons in order to improve treatment times and outcomes,					
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INTRODUCTION

On September 15, 2014, the U.S. Army Medical Research Acquisition Activity (USAMRAA) awarded a 2-year contract to the University of Texas Health Science Center at Houston (UTHealth). This 2-phase project systematically defined the clinical and logistical issues surrounding traditional open vascular surgery and catheter-based hemorrhage control for non-compressible torso hemorrhage (NCTH). The hypothesis was that minimally invasive, device-driven and expert-led NCTH control techniques improve survival compared to traditional open vascular surgery. In addition to UTHealth, Baylor College of Medicine, the University of Texas Health Science Center at San Antonio (UTHSCSA) and the San Antonio Military Medical Center (SAMMC)/US Army Institute of Surgical Research (USAISR) collaborated.

KEYWORDS

Trauma, Vascular, Hemorrhage, Non-compressible Torso Hemorrhage, Coagulation, Mortality

ACCOMPLISHMENTS

What were the major goals of the project?

Goals/Milestones – Phase I

1. Obtain DOD HRPO and local institutional review board (IRB) approvals
2. Conduct retrospective data collection
3. Analysis of retrospective data
4. Hold Delphi Meeting

Goals/Milestones – Phase II

5. Obtain regulatory amendment approvals for prospective study
6. Conduct prospective observational study
7. Data Analysis/Publications

What was accomplished under these goals?

Milestone 1: Obtain USAMRMC HRPO and participating sites' IRB approvals

Y1Q1 UT Houston IRB approval for the retrospective study was received 18-NOV-2014. We submitted the USAMRMC Human Research Protections Office (HRPO) application on 02-DEC-2014 for review and approval. We also sent the UTHealth IRB approval and study documents to participating sites to submit to their local IRB review and approval. Baylor College of Medicine (BCM) and the University of Texas Health Science Center at San Antonio (UTHSCSA) submitted their local IRB applications in Q1.

Y1Q2 USAMRMC HRPO approval for the retrospective study at the UTHealth site was obtained 23-JAN-2015. UTHSCSA obtained their local IRB approval on 12-MAR-2015. BCM also received local IRB approval on 10-APR-2015. San Antonio Military Medical Center (SAMMC) requested that their site be changed to the US Army Institute of Surgical Research (USAISR) because USAISR had more developed human subjects and contracting processes. USAISR submitted documents to their IRB in Q2.

Y1Q3 UTHSCSA received HRPO approval for the retrospective study on 27-MAR-2015 and BCM received HRPO approval on 20-APR-2015.

Y1Q4 USAISR received local IRB and HRPO approval on 22-JUN-2015. UTHealth received local IRB approval for their continuing review on 31-AUG-2015.

Y2Q1 UTHealth received HRPO continuing review acknowledgement for the retrospective study on 09-OCT-2015.

Y2Q2 BCM and UTHSCSA received continuing review approval for the retrospective study from their local IRBs on 19-JAN-2016 and 17-FEB-2016, respectively.

Y2Q3 UTHealth received approval for the retrospective study continuing review on 23-MAY-2016. UTHSCSA and BCM continuing review acknowledgments for the retrospective study were also received from HRPO on 04-APR-2016 and 22-MAR-2016, respectively. USAISR received IRB and HRPO approval and acknowledgement of continuing review on 18-JUN-2016.

Y2Q4 UTHealth received acknowledgement of continuing review for the retrospective study on 17-AUG-2016.

Y3Q1 BCM received continuing review approval for the retrospective study on 20-OCT-2016.

Y3Q2 UTHealth and USHSCSA received continuing review approval for the retrospective study on 17-FEB-2017 and 14-FEB-2017, respectively. HRPO continuing review acknowledgement for the BCM retrospective study was received 07-MAR-2017.

Y3Q3 UTHealth requested continuing review acknowledgement from HRPO for the retrospective study on 09-MAR-2017. HRPO continuing review acknowledgement for the UTHSCSA retrospective study was received 23-MAY-2017.

Y3Q4 USAISR received continuing review approval for the retrospective study on 20-June-2017.

Y4Q1 All regulatory approvals were up-to-date in Y4Q1.

Y4Q2 BCM and UTHealth received HRPO acknowledgment of continuing review for the retrospective study on 22-FEB-2018 and 09-MAR-2018, respectively. UTHSCSA received approval of continuing review on 15-FEB-2018.

Y4Q3 All regulatory approvals were up-to-date in Y4Q3.

Y4Q4 USAISR received continuing review approval for the retrospective study on approximately 20-June-2018, although they haven't sent us a copy of their approval to date. BCM sent in continuing review documents to HRPO this quarter. All other regulatory approvals were up-to-date in Y4Q4.

Y5Q1 As of 31-Aug-2018, the UTHealth IRB revised the continuing review process to conform with the revised Common Rule. Because this study was approved under an expedited process, no further continuing reviews are needed. Documentation was sent to HRPO.

Y5Q2 All regulatory approvals were up-to-date in Y5Q2.

Y5Q3 All regulatory approvals were up-to-date in Y5Q3.

Y5Q4 All regulatory approvals were up-to-date in Y5Q4.

Milestone 2: Initiate retrospective data collection study.

Y1Q1 Before the UTHealth IRB submission, we had a series of internal meetings as well as phone calls and emails with external investigators to discuss, revise, and finalize the protocol and case report forms for the retrospective study. The protocol and case report forms were finalized as of 15-NOV-2014. We also submitted information and study documents to UTHealth's

Sponsored Projects Administration in order to begin drafting of the subcontracts for the three external sites as the next step to initiating data collection.

Y1Q2 The subcontracts with the three sites were drafted by UTHealth's Sponsored Projects Administration and sent to the three external sites as the first step to initiating data collection. The subcontracts were sent to the sites on 07-JAN-2015. Contract negotiation has taken longer than expected and at the end of Y1Q2, all three subcontracts were not yet executed. USAISR has requested a Cooperative Research and Development Agreement (CRADA) and a Data Use Agreement (DUA) for this study instead of the standard Federal Demonstration Partnership (FDP) contract we use for all other sites and projects. We expect that the contracts for BCM and UTHSCSA will be executed in early Q3. Because we have not received approval from the GOR for the change in PI for USAISR, we cannot move forward with the CRADA; however, the DUA can move forward. We have developed a REDCap application for the Phase 1 retrospective study, including a data dictionary, codebook and data entry forms. We are finalizing this database application. Once completed, UTHealth will start entering data into the application.

Y1Q3 UTHealth, UTHSCSA and BCM have begun the trauma registry query and retrospective data review. We received approval from the GOR for the change in PI and research site to USAISR. Contract negotiations continue with USAISR because they are using a Cooperative Research and Development Agreement (CRADA) instead of the standard Federal Demonstration Partnership (FDP) contract we developed for all sites. The Data Use Agreement (DUA) that ISR also required has been executed by both parties. The Program Manager at USISR contacted UTHealth on 25-June-2015 to request additional documents be sent to the Contract Officer at USAMRAA in order for the change in site to take effect. UTHealth sent the documents to her on 29-JUNE-2015. The REDCap application has been finalized and data entry into the system has begun.

Y1Q4 UTHealth requested a status update from the Contract Office at USAMRAA on 13-July-2015, and a response was received on 22-JULY-2015 stating that a modification was being prepared to change the study site. We received a request for additional documents on 08-OCT-2015 from USAMRAA.

Y2Q1 UTHealth, UTHSCSA and BCM completed trauma registry query and retrospective data review and data entry in Y2Q1. 239 patients from UTHealth, 189 from BCM, and 208 from UTHSCSA were enrolled. The Cooperative Research and Development Agreement (CRADA) between UTHealth and USAISR was also fully executed in Y2Q1. USAISR entered registry information on all of their eligible patients (N=51) and are continuing to enter additional detailed data from the medical record abstraction.

Y2Q2 USAISR completed retrospective study data entry in Y2Q2. A total of 683 for the four sites were therefore available for analysis. This number was considerably less than the expected total for enrollment (n=3500) due to the operationalization of the eligibility criteria. The eligibility criteria from both the proposal and the IRB-approved protocol were:

Inclusion Criteria

To be eligible, subjects must meet all of the following:

- 1) Has NCTH defined as

- a. Named axial torso vessel disruption
 - b. Solid organ injury with AIS ≥ 4 (liver, kidney, or spleen) plus concomitant shock or immediate operation
 - c. Thoracic cavity injury (including lung)
 - d. Pelvic fracture with ring disruption
- 2) Estimated age of 15 years or older or greater than/equal to weight of 50 kg if age unknown
 - 3) Admitted to one of four participating Level 1 trauma centers

Exclusion Criteria

Subjects will be excluded if they meet one or more of the following:

- 1) Patients who are <15 years old or under 50 kg body weight if age unknown
- 2) Known pregnancy reported by EMS personnel
- 3) Isolated hip fractures
- 4) Injury resulting from a fall from standing

For the original submitted grant proposal, we received data from all 4 sites in order to estimate the potential number of patients we would be able to enroll in the retrospective using these inclusion and exclusion criteria. Using these criteria only, we estimated that we would enroll 3500 patients. However, in order to operationalize these criteria for the retrospective study using site trauma registries to identify appropriate patients and to get detailed information regarding the specific vessels of interest, the following rules were used at all 4 sites:

- a. Run the following inclusions/exclusions first:
 - i. Inclusions:
 - 1. Age 15 or older
 - 2. Admitted
 - 3. Time of injury < 12 hours from admission
 - a. Not all of our patients have a time of injury in the registry, so we also used the date/time of EMS notification to try to catch any of those patients
 - ii. Exclusions:
 - 1. Prisoners
 - 2. Isolated hip fractures
 - 3. Injury resulting from a fall from standing (< 6 feet)
 - 4. Prisoners, defined as those who have been directly admitted from a correctional facility
- b. Use that data set to separately find the patients with abdominal, thoracic, and pelvic injuries
 - i. Abdominal
 - 1. We searched for patients with AIS ≥ 3 plus base deficit > 4
 - 2. We searched for patients with AIS ≥ 3 plus immediate operation (limited it to patients that went directly from the ER to the OR within 90 minutes of arrival)
 - 3. We then combined those two lists
 - ii. Thoracic
 - 1. We searched for patients with AIS ≥ 3 plus base deficit > 4

2. We searched for patients with AIS ≥ 3 plus immediate operation (limited it to patients that went directly from the ER to the OR within 90 minutes of arrival)
3. We then combined those two lists
- iii. Pelvic
 1. We searched for patients with AIS05 codes equal to: 856161.3, 856162.4, 856163.4, 856164.5, 856171.4, 856172.4, 856173.5, or 856174.5
- iv. Combine the above 3 lists (abdominal, thoracic, and pelvic)
- c. Use that data set to separately find the patients with named axial torso vessel disruption using both AIS codes and ICD9 codes (to try to find as many as possible)
 - i. AIS codes
 1. Thoracic arteries: 420206.4, 420208.4, 420210.5, 420216.5, 420218.6, 420404.3, 420406.3, 420408.4, 421004.3, 421006.3, 421008.5, 421009.6, 421404.3, 421406.3, 421408.4, 422004.2, 422006.2, 422008.3
 2. Thoracic veins: 420602.3, 420604.3, 420606.4, 420608.5, 421202.3, 421204.3, 421206.5, 421207.6, 421602.3, 421604.3, 421606.4, 421802.3, 421804.3, 421806.4, 421808.5, 422202.2, 422204.2, 422206.3
 3. Abdominal arteries: 520204.4, 520206.4, 520208.5, 520404.3, 520406.4, 520408.5, 520604.3, 520606.3, 520608.4, 521104.3, 521106.3, 521108.4, 521404.3, 521406.3, 521408.4, 541828.5
 4. Abdominal veins: 520802.3, 520804.3, 520806.4, 521002.2, 521004.2, 521006.3, 521202.3, 521204.3, 521206.4, 521602.3, 521604.3, 521606.4
 5. Common carotid arteries: 320206.3, 320208.3, 320209.3, 320210.4, 320211.4, 320212.4, 320213.4, 320214.5, 320215.5, 320216.3, 320217.3, 320218.4, 320219.4
 - ii. ICD9 codes
 1. Thorax: 901.0, 901.1, 901.2, 901.3, 901.41, 901.42
 2. Abdomen: 902.0, 902.10, 902.20, 902.22, 902.23, 902.25, 902.31, 902.33, 902.41, 902.42, 902.53, 902.54
 3. Common carotid: 900.01
 - iii. Combine the AIS and ICD9 lists and produced our final patient list.

Using these rules to generate the sampling frame for patients, further exclusions were made if no specifically-named vessels were reported in the medical record. In the prospective study, we will be able to include solid organ injuries as well as vessel injuries.

Y2Q3 We initiated a study of CT data for vascular injuries in order to begin collecting data for questions we had originally planned to address in the prospective study. This substudy uses data only from UTHealth, where we have adequate image storage capabilities, and is approved under the retrospective study UTHealth IRB and HRPO approvals. The plan for this substudy is to accurately quantify the applicable vascular morphometry of the human torso, which can be done

with images previously stored during the retrospective study. For the scan-based measurements, standard imaging software is used to measure diameter and length of the torso vessels and relative distances between major aortic branch vessels as related to aortic zones defined by Stannard, et al. We are also including a CT measurement component in the prospective study at UTHealth to continue this work.

Y2Q4 Data collection, entry and cleaning for the substudy of CT images for vascular injuries was largely completed in Y2Q4. One more field for 100 patients remains to be entered and will be completed in Y3Q1. We also negotiated Data Use Agreements (DUAs) with Madigan Army Medical Center (PI: COL Matthew Martin) and with Denver Health Medical Center (PI: Charles Fox) for their use of the retrospective study data. Both were executed early in Y3Q1.

Y3Q1 The retrospective study was completed as described in the SOW in Y2Q2. Data for the additional CT measurement substudy was completed in this quarter for a training set of data to predict catheter insertion length using external measurements and patient data such as sex, height, weight and body mass index (BMI). We performed a preliminary analysis of the data and identified likely algorithms to predict appropriate insertion to Zones I and III. The developed algorithm will be tested on data from an additional 100 patients that are now being collected. We also executed a Data Use Agreements (DUA) with Madigan Army Medical Center (PI: COL Matthew Martin) for use of the retrospective study data on 26-SEP-2016.

Y3Q2 We performed a preliminary analysis of the CT measurement substudy data and identified likely algorithms to predict appropriate insertion to Zones I and III. We continued to collect data from an additional 100 patients in order to validate the algorithm and expected to complete this additional data collection in early Y3Q3.

Y3Q3 We completed data collection from the additional 100 patients in Y3Q3 and are currently validating the algorithm for the final development of the nomogram which we plan to copyright.

Y3Q4 We have completed data analysis for the CT measurement substudy and the manuscript is currently under development.

Y4Q1 Milestone complete, nothing to report

Y4Q2 Milestone complete, nothing to report

Y4Q3 Milestone complete, nothing to report

Y4Q4 Milestone complete, nothing to report

Y5Q1 Milestone complete, nothing to report

Y5Q2 Milestone complete, nothing to report

Y5Q3 Milestone complete, nothing to report

Y5Q4 Milestone complete, nothing to report

Milestone 3: Analysis of retrospective data

Y2Q1 We identified a Co-Investigator Statistician, Stacia DeSantis, PhD, who worked on preliminary statistical analysis code and programs. She obtained access to the dataset, the data dictionary, the protocol, and updated the statistical plan with assistance from a statistical programmer (T. Jay Greene, MS).

Y2Q2 Data analysis for the Delphi Meeting was completed during this quarter. Additional analysis was undertaken during this quarter as a result of suggestions made at the Delphi Meeting. These analyses will be reported in an upcoming manuscript. Additionally, all attendees of the Delphi Meeting were offered the opportunity to analyze the retrospective data. We are currently working with these external institutions and negotiating Data Use Agreements (DUAs) with them. Our goal is that additional manuscripts and/or abstracts will be submitted as a result of sharing these important data.

Y2Q3 The additional analyses initiated last quarter are ongoing. These analyses will be reported in an upcoming manuscript. Two external institutions (Madigan Army Medical Center and Denver Health Medical Center) requested the retrospective data for their own analysis. The UTHealth Sponsored Projects office completed the draft of the Data Use Agreement, which was sent to the two institutions for negotiation and execution in June 2016.

Y2Q4 We submitted an abstract of the retrospective study to the Eastern Association for the Surgery of Trauma (EAST) Annual Meeting and it was accepted for an oral presentation at the meeting in January. We also drafted a manuscript for the main results of the retrospective study during Y2Q4 and it will be finalized in Y3Q1. Negotiation of the two DUAs continued this quarter.

Y3Q1 The main results manuscript for the retrospective study was finalized and submitted for review during this quarter.

Y3Q2 The main results manuscript for the retrospective study was presented at EAST and is under review at the *Journal of Trauma and Acute Care Surgery*. COL Matthew Martin of Madigan Army Medical Center continued to work on a secondary analysis that hypothesizes that the FAST exam has a high false negative rate when used in the evaluation of NCTH patients. The DUA with Denver Health Medical Center (PI: Charles Fox) was partially executed by UTHealth and awaiting full execution by Denver.

Y3Q3 The main results manuscript for the retrospective study was accepted at the *Journal of Trauma and Acute Care Surgery* on 1-APR-2017. COL Matthew Martin of Madigan Army Medical Center continued to work on a secondary analysis that hypothesizes that the FAST exam has a high false negative rate when used in the evaluation of NCTH patients. The DUA with Denver Health Medical Center (PI: Charles Fox) was fully executed.

Y3Q4 Retrospective data were sent to Denver Health Medical Center on 30-JUN-2017. The main results manuscript for the retrospective study was published in the July edition of the *Journal of*

Trauma and Acute Care Surgery. COL Matthew Martin of Madigan Army Medical Center submitted his secondary analysis that hypothesizing that the FAST exam has a high false negative rate when used in the evaluation of NCTH patients to EAST on 1-JUL-2017.

Y4Q1 The main results manuscript for the retrospective study was accepted at the *Journal of Trauma and Acute Care Surgery* on 1-APR-2017. It will be published in the July edition of the journal.

COL Matthew Martin of Madigan Army Medical Center is continuing to work on a secondary analysis that hypothesizes that the FAST exam has a high false negative rate when used in the evaluation of NCTH patients. The DUA with Denver Health Medical Center (PI: Charles Fox) was fully executed and the data will be sent to Denver in early Y4Q1.

For the CT measurement substudy, we are currently validating the algorithm for the final development of the nonogram which we plan to copyright.

Y4Q2 COL Matthew Martin of Madigan Army Medical Center has access to the retrospective data and continues to perform analysis. Charles Fox, MD, from Denver Health Medical Center is also actively analyzing the retrospective data

A manuscript for the additional CT measurement substudy to predict catheter insertion length using external measurements and patient data such as sex, height, weight and body mass index (BMI) has been under development. Unfortunately, the interpretation of these data has hit a snag because the algorithm to predict catheter insertion length is giving biologically implausible results. Therefore, we are reluctant to publish a manuscript on the algorithm and are having difficulty revising the algorithm because the data are retrospective and confirmatory variables such as actual insertion length are not available. We are not likely to pursue this manuscript any longer, however, higher quality prospective data including actual insertion length are available with the completion of the prospective study in Phase II of this project. Those data do include insertion length, so we will have a gold standard comparison for any algorithm.

Y3Q3 COL Matthew Martin of Madigan Army Medical Center has access to the retrospective data and continues to perform analysis. Charles Fox, MD, from Denver Health Medical Center is also actively analyzing the retrospective data

Y4Q4 Milestone complete. COL Martin and Dr. Charles Fox currently have retrospective data and may pursue other analyses if they desire.

Y5Q1 COL Matthew Martin of Madigan Army Medical Center submitted a manuscript to The American Journal of Surgery entitled “Too Fast, or Not Fast Enough? The FAST Exam in Patients with Non-Compressible Torso Hemorrhage

Y5Q2 COL Martin’s manuscript to The American Journal of Surgery entitled “Too Fast, or Not Fast Enough? The FAST Exam in Patients with Non-Compressible Torso Hemorrhage” was accepted for publication on 06-FEB-2019 and published online this quarter.

Y5Q3 The manuscript reported last quarter from COL Matthew Martin of Madigan Army Medical Center entitled “Too Fast, or Not Fast Enough? The FAST Exam in Patients with Non-Compressible Torso Hemorrhage” was published in The American Journal of Surgery this quarter.

Y5Q4 Milestone complete

Milestone 4: Hold Delphi Meeting

Y2Q1 We updated the list of 20 potential Delphi Panel meeting attendees and received input on additional potential attendees from Col. Todd Rasmussen, an expert in non-compressible torso hemorrhage

Y2Q2 The Delphi Panel Meeting was held on March 7, 2016 at the University of Texas Health Science Center at Houston. A total of 27 people attended the meeting. Attendees included the site investigators and coordinators, trauma and vascular surgeons from civilian and military institutions, and the Houston Data Coordinating Center. The group reviewed the results of the retrospective study and provided input for the upcoming Phase II prospective, observational study. See the Y2Q2 report for the agenda and review of retrospective data used at the Delphi Meeting, notes from the meeting, and a list and picture of participants.

Y2Q3 Milestone complete, nothing to report

Y2Q4 Milestone complete, nothing to report

Y3Q1 Milestone complete, nothing to report

Y3Q2 Milestone complete, nothing to report

Y3Q3 Milestone complete, nothing to report

Y3Q4 Milestone complete, nothing to report

Y4Q1 Milestone complete, nothing to report

Y4Q2 Milestone complete, nothing to report

Y4Q3 Milestone complete, nothing to report

Y4Q4 Milestone complete, nothing to report

Y5Q1 Milestone complete, nothing to report

Y5Q2 Milestone complete, nothing to report

Y5Q3 Milestone complete, nothing to report

Y5Q4 Milestone complete, nothing to report

Milestone 5: Obtain regulatory amendment approvals for prospective study

Y2Q2 We refined a draft of the prospective study protocol based on recommendations and comments at the Delphi Meeting.

Y2Q3 We finalized the Phase II prospective protocol with the other site PIs and staff. The protocol was submitted to the UTHealth IRB on 27-MAY-2016.

Y2Q4 UTHealth received IRB approval on 20-JUL-2016. BCM submitted the protocol to their IRB during Y2Q4. Approval for BCM was received 21-SEP-2016. UTHSCSA applied for IRB reciprocity during this quarter and received approval from the UTHealth IRB on 12-SEP-2016. UTHealth and UTHSCSA submitted their approval documents to HRPO for review. USAISR prepared their documents for submission to the MRMC IRB/HRPO.

Y3Q1 UTHealth and UTHSCSA received HRPO approval for the prospective study on 05-OCT-2016. UTHSCSA used reciprocity and therefore received approval from UTHealth's IRB. BCM received Harris Health System approval on 21-SEPT-2016 (local BCM approval occurred on 17-AUG-2016), and HRPO approval was received on 17-OCT-2016 for the prospective study.

Y3Q2 UTHealth submitted a continuing review application to their local IRB this quarter. USAISR submitted to HRPO for initial review and approval at their site for the prospective study on 17-MAR-2017.

Y3Q3 UTHealth and UTHSCSA received continuing review approval from UTHealth's local IRB this quarter on 27-MAR-2017 and received HRPO acknowledgment on 12-JUN-2017. UTHealth also changed the PI from Dr. Holcomb to Dr. Moore and received approval for the change from the local IRB on 22-MAY-2017. The PI change was acknowledged by HRPO in the 12-JUN-2017 document.

Y3Q4 USAISR received initial local IRB and HRPO approval for the prospective study on 29-JUN-2017.

Y4Q1 All regulatory approvals for the prospective study were up-to-date in Y4Q1

Y4Q2 UTHealth and UTHSCSA (via reciprocity) received continuing review approval for the prospective study on 26-JAN-2018. All other regulatory approvals for the prospective study were up-to-date in Y4Q2

Y4Q3 All regulatory approvals for the prospective study were up-to-date in Y4Q3.

Y4Q4 BCM submitted a continuing review application to their local IRB for the prospective study this quarter. USAISR received continuing review approval on approximately 29-JUN-2018, but have not yet sent UTHealth a copy as of the date of this report. All other regulatory approvals are up-to-date.

Y5Q1 As of 22-OCT-2018, the UTHealth IRB revised the continuing review process to conform with the revised Common Rule. Because this study was approved under an expedited process, no further continuing reviews are needed. Documentation was sent to HRPO.

Y5Q2 All regulatory approvals were up-to-date in Y5Q2.

Y5Q3 All regulatory approvals were up-to-date in Y5Q3.

Y5Q4 All regulatory approvals were up-to-date in Y5Q4.

Milestone 6: Conduct prospective observational study

Y2Q4 We drafted modifications of subawards for BCM and UTHSCSA to extend the date of contract and add the Phase II funds. Both contracts have been executed (BCM on 29-SEP-2016 and UTHSCSA on 30-SEP-2016). We are negotiating a CRADA modification with USAISR for the change in PI from LTC Kevin Chung to LTC Jennifer Gurney. It was signed by UTHealth on 20-SEPT-2016 and we are awaiting signature and full execution by USAISR. In preparation of study initiation, we developed a draft of the Manual of Operations and have circulated it to the 3 external sites for review and comment. We expect to enroll patients in Y3Q1.

Y3Q1 Modifications of subawards for BCM and UTHSCSA to extend the date of contract and add the Phase II funds were executed this quarter (BCM on 29-SEP-2016 and UTHSCSA on 30-SEP-2016). A CRADA modification with USAISR for the change in PI from LTC Kevin Chung to LTC Jennifer Gurney was executed on 27-JUL-2016. A second modification of the CRADA was initiated by USAISR during this quarter. The partially executed CRADA was returned to USAISR on 27-OCT-2016.

Training occurred at UTHealth, UTHSCSA and BCM during Y3Q1. Patient enrollment began at UTHealth on 07-NOV-2016 and 18 patients were enrolled by the end of Y3Q1. UTHSCSA is currently screening patients (started 12-DEC-2016), but had no enrollments by the end of Y3Q1.

Y3Q2 The second modification of the CRADA with USAISR was fully executed on 28-OCT-2016. At UTHealth, 125 patients were screened and 56 patients were enrolled by the end of Y3Q2. UTHSCSA screened 84 patients with 18 enrollments in total by the end of Y3Q2. BCM screened 17 patients and enrolled 7 by the end of Y3Q2.

Y3Q3 At UTHealth, 526 patients were screened and 108 patients were enrolled by the end of Y3Q3. UTHSCSA screened a total of 265 patients and 37 enrollments by the end of Y3Q3. BCM screened 40 patients in total with 15 patients enrolled by the end of Y3Q3. One hundred sixty patients were enrolled by the end of Y3Q3.

Y3Q4 Total screened and enrollment by site at the end of Y3Q4 is shown below.

Site	Screened	Enrolled
UTHealth	1094	153
UTHSCSA	265	37
BCM	144	36
USAISR	127	2
Total	1630	228

Y4Q1 Total enrollment by site at the end of Y4Q1 is shown below.

Site	Enrollment start date	Enrolled
UTHealth	07-NOV-2016	177
UTHSCSA	12-DEC-2016	75
BCM	30-JAN-2017	38
USAISR	27-JUL-2017	4
Total		294

Y4Q2 Enrollment is now complete for the prospective study. Three hundred eighteen total patients were enrolled. Enrollment for all sites ended on 31-JAN-2018 and the data coordinating center at UTHealth will complete major data cleaning by 30-APR-2018.

Site	Enrollment start date	Enrolled
UTHealth	07-NOV-2016	187
UTHSCSA	12-DEC-2016	88
BCM	30-JAN-2017	38
USAISR	27-JUL-2017	5
Total		318

Y4Q3 The data coordinating center at UTHealth is working with the sites on data queries and completing data cleaning. Data from BCM had a high level of missing information, so we spent a large amount of time working with them to get the data cleaned. Preliminary data analysis has begun.

Y4Q4 The team completed initial major data cleaning, developed dummy tables, and drafted five tables for a future publication on the descriptive epidemiology of non-compressible torso hemorrhage (NCTH). Milestone completed as the study has been conducted.

Y5Q1 Milestone completed in Y4Q2, nothing to report.

Y5Q2 Milestone completed in Y4Q2, nothing to report.

Y5Q3 Milestone completed in Y4Q2, nothing to report.

Y5Q4 Milestone completed in Y4Q2, nothing to report.

Milestone 7: Data Analysis/Publications

Y2Q2 We worked on finalizing data analyses and developing a manuscript for the retrospective study.

Y2Q3 We continued to work on finalizing data analyses and developing a manuscript for the retrospective study.

Y2Q4 We submitted an abstract of the retrospective study to the Eastern Association for the Surgery of Trauma (EAST) Annual Meeting on 01-JUL-2016 and it was accepted on 01-AUG-2016 for oral presentation at the meeting. We also drafted a manuscript for this presentation during Y2Q4.

Y3Q1 The main results manuscript for the retrospective study was finalized and submitted for review during this quarter.

Y3Q2 The main results manuscript for the retrospective study was presented at the Eastern Association for the Surgery of Trauma (EAST) Annual Meeting in January 2017. The manuscript was revised and resubmitted for publication in the *Journal of Trauma and Acute Care Surgery* this quarter

Y3Q3 The main results manuscript for the retrospective study was accepted by the *Journal of Trauma and Acute Care Surgery* this quarter. Charles Wade, PhD, also attended the JPC-6/CCCRP FSECC Portfolio In-Progress Review on 02-MAY-2017.

Y3Q4 The main results manuscript for the retrospective study was published in the July edition of the *Journal of Trauma and Acute Care Surgery*.

Chang R, Fox EE, Greene TJ, Eastridge BJ, Gilani R, Chung KK, DeSantis SM, DuBose JJ, Tomasek JS, Fortuna GR Jr, Sams VG, Todd SR, Podbielski JM, Wade CE, Holcomb JB; NCTH Study Group. Multicenter retrospective study of noncompressible torso hemorrhage: Anatomic locations of bleeding and comparison of endovascular versus open approach. *J Trauma Acute Care Surg*. 2017 Jul;83(1):11-18. doi:10.1097/TA.0000000000001530. PubMed PMID: 28632581; PubMed Central PMCID: PMC5484539.

Y4Q1 We are working to complete enrollment, data cleaning and analysis for the prospective study.

Y4Q2 We are working to complete data cleaning and analysis for the prospective study.

Y4Q3 We are working to complete data cleaning and analysis for the prospective study.

Y4Q4 The team completed initial major data cleaning, developed dummy tables, and drafted five tables for a future publication on the descriptive epidemiology of non-compressible torso hemorrhage (NCTH).

Y5Q1 Major data cleaning has been completed and statistical code has been drafted for the main results manuscript. In addition to the 5 dummy tables, we are continuing to work on a more sophisticated analysis evaluating timing of hemorrhage control procedures.

Y5Q2 We are continuing to finalize the main results manuscript as well as refine a more sophisticated analysis evaluating timing of hemorrhage control procedures.

Y5Q3 We are continuing to finalize the main results manuscript, as well as refine a more sophisticated analysis evaluating timing of hemorrhage control procedures. The main results paper will be an evaluation of the location of injuries found in patients with NCTH with recommendations to trauma surgeons regarding which injuries are the most common and amenable to control using endovascular techniques.

We have also discussed combining data from all of our 3 NCTH-related datasets (retrospective NCTH, prospective NCTH and Prytime) to create a larger dataset for analysis to help verify our main hypothesis. Lastly, we are negotiating a Data Use Agreement with the National Trauma Institute (NTI) to send deidentified data from this project to their National Trauma Research Repository (NTRR, W81XWH-15-2-0089) so that others can perform additional secondary analyses.

Y5Q4 We submitted an abstract entitled, “Endovascular Intervention for Non-compressible Truncal Hemorrhage,” representing the main results of the prospective study to Western Trauma.

The Data Use Agreement with NTI was fully executed on 27-SEPT-2019. Deidentified datasets as well as data dictionaries for both the retrospective and prospective studies have been prepared, and they are currently being finalized. Both retrospective and prospective datasets and associated documentation (data dictionaries, case report forms, Manuals of Operations, and protocols) were be transferred to NTI after the project ended.

The main results manuscript was finalized after the end of the project (Appendix 3).

The manuscript of the analysis of timing of HC procedures is still under development and finalization.

What opportunities for training and professional development has the project provided?

Three doctoral students in biostatistics (T. Jay Greene, Jada Johnson, and Xu Xun) as well as two medical residents (Ronald Chang, MD, and Kayla Isbell, MD) have worked on this project and participated in analysis and interpretation of data as part of their training.

How were the results disseminated to communities of interest?

Results were disseminated through the publications and presentations that have been accepted. In addition, the transfer of both datasets to the NTI National Trauma Research Repository facilitates wider use of these data and allows for continued dissemination of results.

What do you plan to do during the next reporting period to accomplish the goals?

Not applicable

IMPACT

What was the impact on the development of the principal discipline(s) of the project?

The results of the retrospective study preliminarily evaluated the location of injuries found in patients with NCTH and identified the most common endovascular procedure with recommendations to trauma surgeons regarding which injuries are the most common and amenable to control using endovascular techniques. The prospective study validated these procedures.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfers?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

CHANGES/PROBLEMS**Changes in approach and reasons for change**

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to report

Changes that had a significant impact on expenditures

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

PRODUCTS

Publications, conference papers, and presentations

Manuscripts

Chang R, Fox EE, Greene TJ, Eastridge BJ, Gilani R, Chung KK, DeSantis SM, DuBose JJ, Tomasek TS, Fortuna GR, Sames VG, Todd SR, Podbielski JM, Wade CE, Holcomb JB and the NCTH Study Group. Multicenter retrospective study of non-compressible torso hemorrhage: anatomic locations of bleeding and comparison of endovascular versus open approach. *J Trauma Acute Care Surg.* 2017;83(1):11-18. PMID: 28632581. PMCID: PMC5484539.

Do WS, Chang R, **Fox EE**. Wade CE, Holcomb JB, Martin MJ; NCTH Study Group. To fast, or not fast enough? The FAST exam in patients with non-compressible torso hemorrhage. *Am J Surg.* 2019 May;217(5):882-886. PMID: 30853094.

Presentations

Chang R, Fox EE, Greene TJ, Eastridge BJ, Gilani R, Chung KK, DeSantis SM, DuBose JJ, Tomasek JS, Fortuna GR, Sams VG, Todd SR, Podbielski JM, Wade CE, Holcomb JB. Multicenter retrospective study of non-compressible torso hemorrhage: anatomic locations of bleeding and comparison of endovascular versus open approach. Eastern Association for the Surgery of Trauma, Hollywood, FL, January 2017.

Website(s) or other Internet site(s)

Nothing to report.

Technologies or techniques

Nothing to report

Inventions, patent applications, and/or licenses

Nothing to report

Other Products

Nothing to report

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Laura J. Moore, MD
Project Role: Principal Investigator
Nearest Person Months Worked: 1
Contribution to Project: Dr. Moore oversaw all aspects of study management and execution for both the retrospective and prospective studies starting April 1, 2017. She oversaw all study staff, regulatory submissions, patient screening, subject enrollment, and data collection. She actively communicated with all clinical sites for this study, coordinated administration across institutions and ensured accurate and timely data collection and transfer.
Funding Source: DOD W81XWH-14-1-0112

Name: Erin Fox, PhD
Project Role: Co-Investigator; Project Manager
Nearest Person Months Worked: 2
Contribution to Project: Dr. Fox oversees the day-to-day communication and overall study coordination for both the retrospective and prospective multisite studies. She ensures timely and accurate reporting, including financial and interim research reports. She participated in the creation of the data management system and the Manual of Operation, data cleaning and integration, and coordination of requested data to research investigators in the retrospective study and will perform similar duties in the prospective study. She coordinated the subcontracts and budgets for the research sites. Dr. Fox is also involved with the analysis of data, interpretation of results, and development of manuscripts for this project.
Funding Source: DOD W81XWH-14-1-0112

Name: Charles Wade, PhD
Project Role: Co-Investigator
Nearest Person Months Worked: 1
Contribution to Project: Dr. Wade participated in the creation of the data management system and the Manual of Operation, data cleaning and integration, and coordination of requested data to research investigators.
Funding Source: DOD W81XWH-14-1-0112

Name: Jeanette Podbielski, RN
Project Role: Clinical Program/Regulatory Director

Nearest Person Months Worked:	1
Contribution to Project:	Ms. Podbielski managed all regulatory aspects of this study. She assisted with study coordination as well as IRB preparation and submission. She managed the activities of the Research Coordinator and Assistant. Ms. Podbielski is the main point of contact for the external sites for regulatory issues, patient enrollment, and data collection.
Funding Source:	DOD W81XWH-14-1-0112
Name:	Denise Hinds, RN
Project Role:	Research Coordinator
Nearest Person Months Worked:	2
Contribution to Project:	Ms. Hinds assisted with all aspects of study coordination, including the attainment and maintenance of all necessary regulatory approvals and guidelines as well as patient enrollment, data collection, data entry, and answering queries at the UTHealth site for the prospective study.
Funding Source:	DOD W81XWH-14-1-0112
Name:	Marc Dipasupil
Project Role:	Research Assistant
Nearest Person Months Worked:	1
Contribution to Project:	Mr. Dipasupil assisted in identifying eligible patients, performing data collection, and entering data at the UTHealth site in the prospective study.
Funding Source:	DOD W81XWH-14-1-0112
Name:	Kandice Motley
Project Role:	Research Assistant
Nearest Person Months Worked:	3
Contribution to Project:	Ms. Motley assisted in identifying eligible patients, performing data collection, and entering data at the UTHealth site in the prospective study.
Funding Source:	DOD W81XWH-14-1-0112
Name:	Christy Allen
Project Role:	Research Assistant
Nearest Person Months Worked:	1
Contribution to Project:	Ms. Allen assisted in identifying eligible patients, performing data collection, and entering data at the UTHealth site in the prospective study.
Funding Source:	DOD W81XWH-14-1-0112
Name:	Tamara Matthew
Project Role:	Research Assistant
Nearest Person Months Worked:	1

Contribution to Project:	Ms. Matthew assisted in identifying eligible patients, performing data collection, and entering data at the UTHealth site in the prospective study.
Funding Source:	DOD W81XWH-14-1-0112
Name:	Xu Xun
Project Role:	Data Manager
Nearest Person Months Worked:	2
Contribution to Project:	Ms. Xun was hired in December 2017 as a Data Manager for CeTIR and has worked on this project to assist with identifying data issues, as well as running queries for data cleaning and management for the prospective study.
Funding Source:	DOD W81XWH-14-1-0112
Name:	Carolyn Grimes, DrPH
Project Role:	Grants and Contracts Specialist
Nearest Person Months Worked:	1
Contribution to Project:	Dr. Grimes has been assisting with financial and contractual management of this study.
Funding Source:	DOD W81XWH-14-1-0112
Name:	Stacia DeSantis, PhD
Project Role:	Co-Investigator (Statistician)
Nearest Person Months Worked:	1
Contribution to Project:	Dr. DeSantis is the lead statistician for this project. She oversees all data management and analysis for both the retrospective and prospective studies.
Funding Source:	DOD W81XWH-14-1-0112
Name:	T. Jay Greene, MS
Project Role:	Graduate Research Assistant (Statistical Programmer)
Nearest Person Months Worked:	1
Contribution to Project:	Mr. Green acted as the statistical programmer for both the retrospective and prospective studies and was supervised by Dr. DeSantis. He left UT in November 2017.
Funding Source:	DOD W81XWH-14-1-0112

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

We reported Dr. Moore's active other support last year, and her current support is as follows:

Title: FiO2 Closed Loop Control in the ZOLL 731 Series Ventilator
Time Commitment: 4%
Agency: University of Cincinnati/ZOLL Medical/USAF/AFMC, Jay Johannigman, MD
Agency POC: S. Theresa Yockey, University of Cincinnati, Sponsored Research Services, 51 Goodman Avenue, Suite 530, Cincinnati, OH 45221-0222; 513-556-4390
Performance Period: 05/2015-05/2018
Role: Principal Investigator
Level of Funding: \$220,000
Goals: To demonstrate that physiologic closed-loop control (PCLC) is at least as safe and effective as manual control in keeping hemoglobin oxygen saturation (SpO₂) within the target range of 92-96%.

Title: Multicenter, Observational Clinical Study of the ER-REBOA Catheter
Time Commitment: 25%
Agency: Prytime Medical Devices, Inc./USAMMA/W911QY-15-C-0099
Agency POC: David Spencer, CEO, Prytime Medical Devices, Inc., 229 N. Main Street, Boerne, TX 78006; dspencer@prytimemedical.com
Performance Period: 04/2017-06/2018
Role: Principal Investigator
Level of Funding: \$1,248,137
Goals: The purpose of this multicenter, prospective, observational study is to collect detailed information at selected Level 1 trauma centers currently utilizing the Prytime REBOA catheter as part of their standard clinical practice.

What other organizations were involved as partners?

Baylor College of Medicine
Houston, TX
Research collaborator

University of Texas Health Science Center at San Antonio
San Antonio, TX
Research collaborator

US Army Institute of Surgical Research
San Antonio, TX
Research collaborator

SPECIAL REPORTING REQUIREMENTS

Quad Chart uploaded as Appendix 1.

APPENDIX 1

Hemorrhage Control for Major Traumatic Vascular Injuries

EDMS: 5840 and Quad Chart for Final Report
W81XWH-14-1-0112



PI: Laura J. Moore, MD **Org:** University of Texas Health Science Center at Houston **Award Amount:** \$1,991,317

Study Aims

- Determine current practice patterns for the treatment of patients with non-compressible torso hemorrhage (NCTH) among 4 clinical sites using a retrospective study design;
- Conduct a 2-day Delphi Panel meeting of military and civilian experts to gain consensus regarding anatomic, technology, credentialing, competency, and training issues for catheter-based hemorrhage control and inform the development of the prospective study.
- Conduct a 4-site prospective observational study to test the hypothesis that less-invasive device-driven and expert-led hemorrhage control techniques improve survival in NCTH patients and definitively inform development of catheters, devices and training required for catheter-based hemorrhage control.

Approach

This is a 2-phase study which will include a retrospective study and Delphi Meeting in Phase I, then a prospective study in Phase II informed by the Phase I activities.



These pictures represent the care of the severely injured NCTH patient, which will be studied in this project.

Accomplishments this quarter: Finalization of main results manuscript for prospective study.
Transfer of data to NTI after completion of project.

Timeline and Cost

Activities	Y1	Y2	Y3	Y4	Y5
Phase 1 milestones	→				
Obtain IRB approvals for prospective study		→			
Conduct prospective study			→		
Data analysis/ publication				→	
Estimated Budget (\$K)	994	996	EWOF 1	EWOF 2	EWOF 4

Goals/Milestones

CY14 -15 Goals – Phase I

- ☐ Obtain DoD HPRO and local IRB approvals
- ☐ Conduct retrospective data collection
- ☐ Analysis of retrospective data
- ☐ Hold Delphi Panel meeting

CY15-16 and EWOFF Goals – Phase II

- ☐ Obtain regulatory approvals for prospective study
- ☐ Conduct prospective observational study
- ☐ Data Analysis/Publications

Comments/Challenges/Issues/Concerns

- The prospective study has been completed as well as data analysis and manuscript development. There are no financial or scientific concerns.

Budget Expenditure to Date

Projected Expenditure: Y5Q4 \$0K; YTD \$0K; ITD \$1,991K

Estimated Actual Expenditure: Y5Q4: \$44K; YTD \$183K; ITD \$1,991K

Updated: December 14, 2019

APPENDIX 2. Products (manuscripts)

Multicenter retrospective study of noncompressible torso hemorrhage: Anatomic locations of bleeding and comparison of endovascular versus open approach

Ronald Chang, MD, Erin E. Fox, PhD, Thomas J. Greene, MPH, Brian J. Eastridge, MD, Ramyar Gilani, MD, Kevin K. Chung, MD, Stacia M. DeSantis, PhD, Joseph J. DuBose, MD, Jeffrey S. Tomasek, MD, Gerald R. Fortuna, Jr., MD, Valerie G. Sams, MD, S. Rob Todd, MD, Jeanette M. Podbielski, RN, Charles E. Wade, PhD, John B. Holcomb, MD, and the NCTH Study Group, Houston, Texas

BACKGROUND:	Rational development of technology for rapid control of noncompressible torso hemorrhage (NCTH) requires detailed understanding of what is bleeding. Our objectives were to describe the anatomic location of truncal bleeding in patients presenting with NCTH and compare endovascular (ENDO) management versus open (OPEN) management.
METHODS:	This is a retrospective study of adult trauma patients with NCTH admitted to four urban Level I trauma centers in the Houston and San Antonio metropolitan areas in 2008 to 2012. Inclusion criteria include named axial torso vessel disruption, Abbreviated Injury Scale chest or abdomen score of 3 or higher with shock (base excess, <-4) or truncal operation in 90 minutes or less, or pelvic fracture with ring disruption. Exclusion criteria include isolated hip fractures, falls from standing, or prehospital cardiopulmonary resuscitation. After dichotomizing into OPEN, ENDO, and resuscitative thoracotomy (RT) groups based on the initial approach to control NCTH, a mixed-effects Poisson regression with robust error variance (controlling for age, mechanism, Injury Severity Score, shock, hypotension, and severe head injury as fixed effects and site as a random effect) was used to test the hypothesis that ENDO was associated with reduced in-hospital mortality in NCTH patients.
RESULTS:	Five hundred forty-three patients with NCTH underwent ENDO (n = 166, 31%), OPEN (n = 309, 57%), or RT (n = 68, 12%). Anatomic bleeding locations were 25% chest, 41% abdomen, and 31% pelvis. ENDO was used to treat relatively few types of vascular injuries, whereas OPEN and RT injuries were more diverse. ENDO patients had more blunt trauma (95% vs. 34% vs. 32%); severe injuries (median Injury Severity Score, 34 vs. 27 vs. 21), and increased time to intervention (median, 298 vs. 92 vs. 51 minutes) compared with OPEN and RT. Mortality was 15% versus 20% versus 79%. ENDO was associated with decreased mortality compared to OPEN (relative risk, 0.58; 95% confidence interval, 0.46–0.73).
CONCLUSION:	Although ENDO may reduce mortality in NCTH patients, significant group differences limit the generalizability of this finding. (<i>J Trauma Acute Care Surg.</i> 2017;83: 11–18. Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.)
LEVEL OF EVIDENCE:	Therapeutic, level V.
KEY WORDS:	Noncompressible torso hemorrhage; angioembolization; endovascular hemorrhage control.

Hemorrhage is the leading cause of potentially preventable civilian^{1,2} and military³ trauma deaths. In contrast to other causes of trauma death, exsanguination occurs rapidly (median of 2–3 hours after presentation).^{4–8} Although great progress

has been made in the rapid control of compressible hemorrhage, especially the use of tourniquets for extremity hemorrhage,^{9–11} initial management of noncompressible torso hemorrhage (NCTH) from thoracic, abdominal, and pelvic sources still presents a significant challenge.^{11,12} A retrospective review of 4,596 combat casualty mortalities from 2001 to 2011 in Afghanistan and Iraq found that 24% of deaths were potentially preventable and related to delayed or lack of hemorrhage control. Of the potentially preventable deaths, 67% were due to NCTH.¹¹ An epidemiologic study of the National Trauma Data Bank found that patients admitted to civilian trauma centers with NCTH and hypotension had nearly 50% mortality.¹²

Until recently, expeditious open (OPEN) thoracotomy and/or laparotomy were required for patients in hemorrhagic shock. Endovascular (ENDO) interventions were reserved for patients who were stable enough to undergo diagnostic studies revealing the injured vessel. The advent of hybrid operating rooms, where OPEN and ENDO techniques can be used as needed, has made possible the more frequent use of minimally invasive approaches for definitive control of NCTH in severely and multiply-injured patients.¹³ However, both precise anatomic descriptions of the

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Published online: April 27, 2017.

From the Center for Translational Injury Research (R.C., E.E.F., J.S.T., J.M.P., C.E.W., J.B.H.), Department of Surgery (R.C., E.E.F., C.E.W., J.B.H.), McGovern Medical School; Department of Biostatistics (T.J.G., S.M.D.), School of Public Health, Department of Surgery (B.J.E.), University of Texas Health Science Center at San Antonio, San Antonio; Michael E. DeBakey Department of Surgery (R.G., S.R.T.), Baylor College of Medicine, Houston; United States Army Institute of Surgical Research (K.K.C.); San Antonio Military Medical Center (V.G.S.), Fort Sam Houston; and Department of Cardiothoracic and Vascular Surgery (J.J.D., G.R.F., McGovern Medical School, University of Texas Health Science Center at Houston, Houston, Texas).

This study was presented at the 30th EAST Annual Assembly on January 13, 2017. Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jtrauma.com).

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J Trauma Acute Care Surg
Volume 83, Number 1

source(s) of NCTH and comparisons of ENDO versus OPEN techniques for hemorrhage control are lacking. The objective of this study was twofold: first, to describe the precise anatomic locations of bleeding in a population of adult trauma patients with NCTH, and second, to test the hypothesis that the ENDO versus OPEN approach was associated with reduced mortality in trauma patients presenting with NCTH.

PATIENTS AND METHODS

Study Design

Approval was obtained from the institutional review boards of all four study sites: the University of Texas Health Science Center at Houston (UTHealth), Baylor College of Medicine, the University of Texas Health Science Center at San Antonio, and the San Antonio Military Medical Center as well as the Human Research Protections Office of the US Army Medical Research and Materiel Command. The four study sites represent all of the adult Level I trauma centers for the Houston and San Antonio metropolitan areas; they collectively serve a population of 5.85 million,^{14,15} or 2.5% of the US adult population.¹⁶

Each institutional trauma registry was queried to identify trauma patients who presented between 2008 and 2012 with NCTH defined as (1) named axial torso vessel disruption, (2) Abbreviated Injury Scale (AIS) chest or abdomen score of 3 or greater with concomitant shock (base excess, ≤ -4) or emergent operation (≤ 90 minutes after presentation), or (3) pelvic fracture with ring disruption. Patients who had an isolated hip fracture or isolated fall from standing were excluded. Demographic information, admission vital signs and laboratory studies, AIS and Injury Severity Score (ISS), transfusion of blood products, intensive care unit (ICU)-free days, and mortality were obtained from the institutional trauma registry and/or medical record. Cause of death was obtained from the institutional trauma registry. Radiological and/or operative reports were reviewed to describe as specifically as possible the anatomic location of NCTH or the specific vessel injured. Patients were divided into three groups based on the initial approach to hemorrhage control: OPEN (without resuscitative thoracotomy [RT]), ENDO (including REBOA), and RT. RT patients were grouped separately due to the ramifications of this therapy. Patients who did not undergo one of these procedures or who had prehospital cardiopulmonary resuscitation were excluded. Patients with documented OPEN and ENDO procedures for initial control of one or more sources of NCTH were categorized as the more invasive modality (OPEN). Study data were collected and managed at UTHealth using Research Electronic Data Capture,¹⁷ a secure, Web-based application designed to support data capture for research studies.

Statistical Analysis

Statistical analysis was performed using Stata 14.1 (StataCorp LP, College Station, TX). Data are reported as median values with interquartile range or proportions as appropriate. Categorical data were analyzed by the χ^2 test or Fisher's exact test for categories with five patients or less. Nonparametric comparisons of continuous variables were performed using the Kruskal-Wallis test. If significant, *post hoc* pairwise comparisons with Holm-Bonferroni adjustments were performed using

the Wilcoxon rank-sum test for continuous data and χ^2 or Fisher's exact test for categorical data. To test the hypothesis that ENDO was associated with decreased in-hospital mortality compared with OPEN, we used a mixed-effects Poisson regression with robust error variance, which has been described as a method to estimate relative risks (RR) for a binary outcome.¹⁸ We controlled for age, ISS, mechanism, severe head injury (AIS head ≥ 3), shock (base excess, ≤ 4 mEq/L), and hypotension (systolic blood pressure [SBP], < 90 mm Hg) as fixed effects and site as a random effect. Subgroup analyses were performed based on the body cavity of hemorrhage (chest, abdomen, or pelvis). Missing base excess and SBP data were imputed with predictive mean matching (20 imputations) using age, ISS, AIS scores, mechanism, and treatment (ENDO vs. OPEN vs. RT). An alpha level of 0.05 was used for all statistical tests.

RESULTS

Demographics

During the 5-year study period, 678 patients with NCTH were included. A total of 135 patients were excluded (56 with prehospital cardiopulmonary resuscitation, 54 who did not undergo a procedure for hemorrhage control, 15 who died before an intervention was performed, and 10 with missing procedure data), leaving 543 (80%) patients who underwent ENDO ($n = 166$, 31%), OPEN ($n = 309$, 57%), or RT ($n = 68$, 12%). The number of included patients per site was 203, 171, 128, and 41, respectively. Use of ENDO significantly increased from 21% in 2008 to 41% in 2012 ($p < 0.01$). Only one patient in the ENDO group underwent REBOA. Nine (3%) OPEN patients also underwent an ENDO procedure for initial control of NCTH.

Demographics and admission parameters are summarized in Table 1. Patients in the ENDO group were older, had higher incidence of blunt mechanism, and had higher ISS, as well as much longer times to intervention than OPEN or RT patients.

Blood Product Transfusions and Mortality

Outcomes data are summarized in Table 2. The mortality per site was 29%, 30%, 13%, and 37%, respectively ($p < 0.01$). Transfusions were performed according to institutional practice without sharing of protocols. ENDO patients received the fewest 24-hour RBCs, whereas plasma and platelet transfusions were not different between groups. ENDO patients had the highest 24-hour plasma-RBC ratio. Both median 24-hour plasma-RBC (1.00 vs. 0.14 vs. 0.70 vs. 0.63) and platelet-RBC (0.67 vs. 0.00 vs. 0.28 vs. 0.53) varied significantly between sites (both $p < 0.05$).

Exsanguination was significantly less frequent as a cause of death in ENDO patients (40% vs. 67% vs. 89%), although exsanguination was the most commonly cited cause of death for all groups. TBI and sepsis/multiple organ failure were the second and third most common causes of death in the ENDO group and were more common compared with the OPEN and RT groups. Time to death was significantly longer in ENDO patients (median, 66 vs. 4 vs. 2 hours). Incidence of rebleeding requiring unplanned interventions and ICU-free days between ENDO and OPEN groups were similar. The procedure performed to address rebleeding (OPEN versus ENDO) was not available.

TABLE 1. Demographics and Admission Parameters

Variables	Missing	ENDO (n = 166, 31%)	OPEN (n = 309, 57%)	RT (n = 68, 12%)	p
Age, y	0 (0%)	38 (24–52)	31 (23–42)	31 (23–44)	<0.01
Male	0 (0%)	126 (76%)	255 (83%)	56 (82%)	0.20
Blunt	0 (0%)	157 (95%)	104 (34%)	22 (32%)	<0.001
AIS head ≥3	0 (0%)	52 (31%)	38 (12%)	15 (22%)	<0.001
AIS chest ≥3	0 (0%)	116 (70%)	142 (46%)	40 (59%)	<0.001
AIS abdomen ≥3	0 (0%)	127 (77%)	249 (81%)	52 (76%)	0.51
AIS extremity ≥3	0 (0%)	95 (57%)	68 (22%)	29 (29%)	<0.001
ISS	0 (0%)	34 (25–41)	21 (16–30)	27 (24–43)	<0.001
ED SBP, mm Hg	44 (8%)	107 (85–129)	102 (82–125)	91 (74–127)	0.23
ED hypotension*	44 (8%)	48 (30%)	90 (32%)	23 (43%)	0.20
ED GCS	19 (3%)	14 (3–15)	15 (8–15)	8 (3–14)	<0.001
ED base excess, mEq/L	28 (5%)	−7 (−11 to −4)	−7 (−13 to −4)	−16 (−21 to −12)	<0.001
ED shock**	28 (5%)	116 (73%)	213 (71%)	54 (95%)	0.001
ED hemoglobin, g/dL	27 (5%)	11.9 (10.5–13.3)	12.0 (10.4–13.3)	10.9 (9.2–12.6)	<0.01
ED platelet count ($\times 10^9/L$)	43 (8%)	227 (172–289)	216 (155–273)	199 (132–264)	0.06
Time to intervention, min	95 (18%)	298 (200–683)	92 (61–163)	51 (33–89)	<0.001

ED, emergency department; GCS, Glasgow Coma Scale.

*SBP, <90 mm Hg.

**Base excess, < −4 mEq/L.

Description of Vascular Injury

Anatomic locations of bleeding are summarized in Table 3. The overall distribution of NCTH was chest 25%, abdomen 41%, pelvis 31%, and unspecified 3%. Injuries in the ENDO group were most common in the pelvis, whereas injuries in the OPEN and RT groups were most commonly abdominal. In the ENDO group, two anatomic locations of bleeding—the descending thoracic aorta (n = 44, 27%) and the internal iliac arteries (n = 51, 31%)—accounted for over half of all ENDO interventions. Only five (3%) ENDO interventions were for venous bleeding. In contrast, sources of bleeding in the OPEN and RT

groups were much more diverse. Many relatively common bleeding sources in the OPEN and RT groups had no representation in the ENDO group.

Multivariable Analysis

Predictive mean matching with age, ISS, AIS scores, mechanism, and treatment were used to impute missing SBP and base excess values for 65 (12%) patients. After imputation, the distribution of SBP and base excess values were unchanged. We constructed a mixed-effects Poisson regression with robust error variance controlling for age, ISS, mechanism, severe head

TABLE 2. Outcomes

Variable	Missing	ENDO (n = 166, 31%)	OPEN (n = 309, 57%)	RT (n = 68, 12%)	p
24 h RBC (units)	3 (<1%)	4 (1–11)	8 (3–17)	14 (7–22)	<0.001
24 h Plasma (units)	3 (<1%)	3 (0–10)	4 (0–12)	3 (0–12)	0.38
24 h Plt (units)	3 (<1%)	0 (0–12)	0 (0–6)	1 (0–6)	0.83
24 h Plasma-RBC ratio	3 (<1%)	0.86 (0.25–1.15)	0.67 (0.20–1.00)	0.29 (0–0.69)	<0.001
24 h Plt-RBC ratio	3 (<1%)	0.50 (0–1)	0.14 (0–0.75)	0.08 (0–0.38)	0.20
Rebleeding	3 (<1%)	9 (5%)	9 (3%)	4 (6%)	0.16
ICU-free days	0 (0%)	18 (4–25)	22 (0–27)	0 (0–0)	<0.001
Death	0 (0%)	25 (15%)	63 (20%)	54 (79%)	<0.001
Causes of death*	0 (0%)				
Exsanguination		10 (40%)	42 (67%)	48 (89%)	<0.001
TBI		9 (36%)	6 (10%)	1 (2%)	<0.001
Respiratory		2 (8%)	1 (2%)	2 (4%)	0.34
Sepsis/MOF		8 (32%)	11 (19%)	3 (6%)	0.01
MI/stroke		2 (8%)	3 (5%)	1 (2%)	0.42
Pulmonary embolism		1 (3%)	0 (0%)	0 (0%)	0.18
Time to death, h	0 (0%)	66 (7–185)	4 (2–25)	2 (1–6)	<0.001

*Not mutually exclusive.

RBC, red blood cells; Plt, platelets; MOF, multiple organ failure; MI, myocardial infarction.

TABLE 3. Anatomic Location of Vascular Injury

	ENDO (n = 166, 31%)	OPEN (n = 309, 57%)	RT (n = 68, 12%)
Chest	50 (30.1%)	66 (21.4%)	21 (30.9%)
Pulmonary artery		5 (1.6%)	1 (1.5%)
Ascending aorta	1 (0.6%)	7 (2.3%)	3 (4.4%)
Aortic arch	1 (0.6%)	1 (0.3%)	1 (1.5%)
Innominate artery		2 (0.6%)	
Right subclavian artery	2 (1.2%)	7 (2.3%)	1 (1.5%)
Intrathoracic right common carotid artery		2 (0.6%)	
Intrathoracic left common carotid artery		3 (1%)	
Left subclavian artery	2 (1.2%)	4 (1.3%)	1 (1.5%)
Intercostal/internal thoracic arteries		17 (5.5%)	
Descending thoracic aorta	44 (26.5%)	8 (2.6%)	10 (14.7%)
Pulmonary vein		2 (0.6%)	1 (1.5%)
Superior vena cava		1 (0.3%)	2 (2.9%)
Innominate vein		3 (1%)	
Subclavian vein		4 (1.3%)	1 (1.5%)
Abdomen	37 (22.3%)	154 (49.8%)	34 (50.0%)
Abdominal aorta		6 (1.9%)	4 (5.9%)
Visceral abdominal aorta		1 (0.3%)	1 (1.5%)
Celiac artery		2 (0.6%)	
Common hepatic artery	7 (4.2%)	10 (3.2%)	1 (1.5%)
L hepatic artery	2 (1.2%)	1 (0.3%)	
R hepatic artery	4 (2.4%)	1 (0.3%)	
Splenic artery	6 (3.6%)	4 (1.3%)	1 (1.5%)
Left gastric artery	1 (0.6%)	3 (1%)	
Gastroepiploic artery		3 (1%)	
Superior mesenteric artery		20 (6.5%)	1 (1.5%)
Ileocolic artery		1 (0.3%)	
Inferior mesenteric artery		2 (0.6%)	1 (1.5%)
Other abdominal visceral artery		13 (4.2%)	1 (1.5%)
Renal artery	14 (8.4%)	8 (2.6%)	2 (2.9%)
Infrarenal aorta	1 (0.6%)	4 (1.3%)	1 (1.5%)
Suprarenal/subhepatic inferior vena cava		16 (5.2%)	6 (8.8%)
Retrohepatic inferior vena cava		8 (2.6%)	2 (2.9%)
Portal vein	1 (0.6%)	5 (1.6%)	2 (2.9%)
Splenic vein		9 (2.9%)	1 (1.5%)
Superior mesenteric vein		11 (3.6%)	1 (1.5%)
Renal vein		5 (1.6%)	1 (1.5%)
Gonadal vein	1 (0.6%)	4 (1.3%)	
Infrarenal inferior vena cava		14 (4.5%)	6 (8.8%)
Inferior vena cava, unspecified		3 (1%)	2 (2.9%)
Pelvis	76 (45.8%)	81 (26.2%)	10 (14.7%)
Common iliac artery	1 (0.6%)	7 (2.3%)	3 (4.4%)
External iliac artery	4 (2.4%)	12 (3.9%)	2 (2.9%)
Internal iliac artery	51 (30.7%)	17 (5.5%)	5 (7.4%)
Internal iliac artery branches	17 (10.2%)	13 (4.2%)	
Common iliac vein		18 (5.8%)	
External iliac vein		11 (3.6%)	
Internal iliac vein	3 (1.8%)	3 (1%)	
Unknown	3 (1.8%)	8 (2.6%)	3 (4.4%)

injury (AIS head, ≥ 3), shock (base excess, ≤ 4 mEq/L), and hypotension (SBP, < 90 mm Hg) as fixed effects and site as a random effect and found that ENDO was associated with reduced in-hospital mortality compared with OPEN (RR, 0.58; 95%

confidence interval [CI], 0.46–0.73), whereas RT was associated with increased mortality compared with OPEN (RR, 3.00; 95% CI, 1.84–4.90). We found similar results in a model analyzing only patients with nonmissing SBP and base excess data and

in a model, where OPEN patients, who underwent a concurrent ENDO procedure ($n = 9$, 3%), were moved to the ENDO group (see Supplemental Digital Content 1, <http://links.lww.com/TA/A951>).

Because a large proportion of ENDO interventions were performed after blunt thoracic aortic injury (BTAI), possibly for low-grade injuries, we performed a sensitivity analysis using the above covariates and imputed values after excluding patients with BTAI. In this cohort ($n = 488$), ENDO was associated with reduced mortality compared with OPEN (RR, 0.67; 95% CI, 0.54–0.83).

ENDO Versus OPEN in the Chest Versus Abdomen Versus Pelvis

Exploratory analyses of bleeding for each body cavity (chest, abdomen, or pelvis) were performed (Fig. 1). Using the same covariates as above, use of ENDO was associated with reduced mortality in the chest ($n = 137$; RR, 0.31; 95% CI, 0.15–0.64) and abdomen ($n = 225$; RR, 0.38; 95% CI, 0.34–0.44), but not pelvis ($n = 167$; RR, 1.10; 95% CI, 0.32–3.79).

Diagnostic studies were performed for all multivariable models (see Supplemental Digital Content 1, <http://links.lww.com/TA/A951>). In terms of global goodness-of-fit, χ^2 tests of the deviance statistic were not significant ($p > 0.05$). Visual inspection of deviance residuals versus predicted values revealed no outliers, and all residuals were within two standard deviations of the mean. Due to the dichotomous outcome, the residuals were not expected to be normally distributed. Instead, we used our model to generate simulated data; visual comparison of actual versus simulated residuals did not reveal large deviations.

DISCUSSION

We performed a retrospective study of adult patients with NCTH presenting to four Level I trauma centers from 2008 to 2012, which collectively represent all of the adult Level I centers in the Houston and San Antonio metropolitan areas. The most common cause of death of all patients in this study was exsanguination (70%); median time to exsanguination was 2 hours

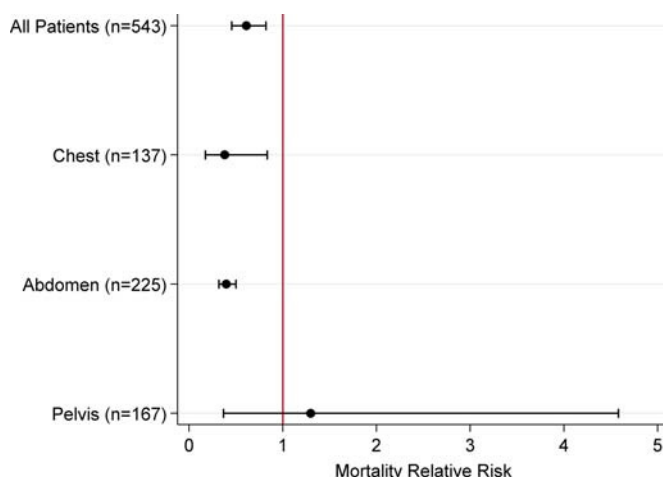


Figure 1. RR of mortality in ENDO versus OPEN groups for all included patients and each anatomic region of bleeding.

(interquartile range, 1 to 5 hours), consistent with other studies of hemorrhaging trauma patients,^{4–8} and a testament to the time criticality of hemorrhage control. Using mixed-effects P, we found that ENDO was significantly associated with decreased mortality compared with OPEN in all patients. However, there were significant preintervention disparities between ENDO and OPEN patients. Although ENDO patients had higher ISS, OPEN patients had significantly decreased time to intervention, increased 24-hour RBC transfusions despite shorter time to death, and increased incidence of exsanguination, all consistent with the notion that OPEN patients had substantial on-going hemorrhage at admission, while ENDO patients—although in shock—were stable enough to undergo an ENDO procedure. There were no differences in 24-hour plasma or platelet transfusions, but this may have been due to survivor bias.

Given the ubiquity of ENDO therapy in the elective treatment of vascular disease and its successful use in vascular emergencies, such as ruptured abdominal aortic aneurysm,¹⁹ definitive ENDO treatment of traumatic hemorrhage is becoming increasingly viable.²⁰ One of the first areas where ENDO treatment was identified as potentially advantageous was bleeding from pelvic fractures.^{21,22} Guidelines from the Eastern Association for the Surgery of Trauma (EAST), published in 2011, recommend pursuing ENDO management for any hemodynamically unstable patient with hemorrhage related to pelvic fractures without significant bleeding from another source (Level I recommendation), whereas preperitoneal packing is recommended as salvage therapy after failure of ENDO therapy (Level III recommendation).²³ On the other hand, a more recent guideline from the Western Trauma Association, published in 2016, describes several “complimentary, and not mutually exclusive, options” including pelvic stabilization, preperitoneal packing, REBOA, and ENDO therapy,²⁴ without clear superiority of any one strategy. A recent multicenter prospective observational study of 1,339 patients with pelvic fracture found that angioembolization and external pelvic fixation were the most common hemorrhage control techniques for arterial and venous bleeding, respectively.²⁵ Whereas the subgroup with hemorrhagic shock had 32% mortality, a recent single-institution observational study by Burlew et al.²⁶ found that preperitoneal packing as first-line therapy for 128 patients with hemorrhagic shock from unstable pelvic fractures was associated with mortality of only 21%, challenging the notion that preperitoneal packing should be relegated to salvage therapy. In the present study, mortality in patients with hemorrhagic shock from pelvic hemorrhage was 27%. We found that use of ENDO for pelvic hemorrhage was not associated with improved odds of survival on within-group multiple logistic regression. This was likely because ENDO patients with the most significant hemorrhage were bleeding from the pelvis, consistent with EAST guidelines. Among all 166 ENDO patients, seven (4%) patients exsanguinated within 6 hours of admission, and six of these had bleeding from the pelvis.

In the chest and abdomen, current guidelines recommend that ENDO therapy should be reserved for hemodynamically stable patients, whereas unstable patients should undergo OPEN hemorrhage control.^{27–32} Specifically, current data suggest that delayed repair of low-grade (1 or 2) BTAIs is safe, and ENDO therapy is recommended as first-line treatment by 2015 EAST guidelines.²⁷ Delayed repair of BTAI is justified in the multiple

injuries patient where more immediate lifesaving interventions (e.g., emergent laparotomy or craniotomy) are prioritized, and the aortic injury is temporized by medical blood pressure control before definitive repair.²⁷ However, patients with high-grade (3 or 4) blunt aortic injuries should not be considered for delayed repair.²⁸ Current EAST and Western Trauma Association guidelines recommend ENDO intervention for blunt hepatic^{29,30} and splenic^{31,32} injury only in hemodynamically stable patients. In the present study, ENDO was associated with reduced mortality in the chest and abdomen.

We found that less than 1% of venous injuries were treated by ENDO technique. Disruption of larger and more centrally located veins is required for significant venous hemorrhage due to the lower pressure in the venous system. Patients with injury of large veins often present in profound hemorrhagic shock and are not stable enough to undergo ENDO intervention. At the same time, the ENDO treatment of major venous disruption, such as caval³³ or portal venous injury,³⁴ is not well described.

One impetus for this study is to generate data to inform the rational development of prehospital NCTH control devices or the prehospital implementation of existing devices (e.g., REBOA). Such devices could save many lives in both the civilian and military sectors in much the same way as the extremity tourniquet,³⁵ especially if applied early³⁶ and before the onset of shock.^{9–11} However, the danger is that any device which occludes or tamponades blood flow may exacerbate hemorrhage proximal to the occlusion. Therefore, it is essential to establish the anatomic source of NCTH (or at least rule out proximal hemorrhage) if such a device is to be used safely. For example, Hurley and Holcomb³⁷ performed a retrospective review of 402 patients who underwent emergent laparotomy at a single Level I trauma center, and found that 9% of patients would have benefited from prehospital application of the abdominal aortic junctional tourniquet, because the bleeding source was distal to the aortic bifurcation.

The primary limitation of this study was confounding by indication bias. ENDO interventions were performed almost exclusively for arterial bleeding and for predominantly few anatomic locations. As a whole, ENDO patients had significantly longer times to intervention, longer times to death, and decreased incidence of exsanguination—all suggesting that ENDO patients were generally hemodynamically stable enough for an ENDO procedure, whereas OPEN patients more often had substantial ongoing hemorrhage at time of admission. Exceptions included patients with substantial pelvic hemorrhage who underwent ENDO. Indicators of response to initial resuscitation—such as number of blood products transfused within the first few hours after admission, presence of computed tomography scan before definitive hemorrhage control, and perioperative vital signs or laboratory data—could have been used to stratify patients by degree of ongoing hemorrhage, but were unfortunately not available for this retrospective study. The ENDO group likely included patients with low-grade injury who were at low risk for hemorrhage, but we lacked data regarding the grade of blunt arterial injury to exclude these patients. Another limitation is that only one patient underwent REBOA during this period. The use of REBOA is increasing, is safe in high volume-centers,³⁸ and is at least as effective as RT in achieving aortic occlusion without the morbidity of a highly invasive procedure.³⁹

It is unclear what impact REBOA has in the decision making of ENDO versus OPEN control of NCTH, and this should be investigated in future studies. It is also unknown how many OPEN patients underwent exploration primarily for identification and repair of nonvascular injuries (e.g., bowel injuries) with incidental intraoperative control of hemorrhage. However, there were likely few such patients, given that OPEN patients had evidence of increased on-going hemorrhage as described above. Additionally, we observed a strong association between ENDO and decreased mortality, whereas a significant number of OPEN patients who were at low risk for exsanguination would have diluted this association. Although we sought to identify all adult patients with significant NCTH who survived to hospital presentation, this study does not include those successfully managed at a non-Level I facility, or those who presented to a non-Level I facility and died before transfer. Comprehensive autopsy studies will be required to definitively address the magnitude of this problem.

In conclusion, use of ENDO techniques for nonelective indications is increasing. In this study of patients with NCTH, ENDO treatment was used predominantly after blunt mechanism, in a much more delayed fashion, and for a narrower range of anatomic injuries compared to OPEN hemorrhage control. Its use seems consistent with current guidelines. Although ENDO treatment in this study was significantly associated with decreased mortality in all patients, significant between-group differences limit the generalizability of this finding.

AUTHORSHIP

E.E.F., B.J.E., R.G., K.K.C., J.M.P., C.E.W., and J.B.H. participated in the study inception and design. E.E.F., B.J.E., R.G., K.K.C., S.M.D., J.J.D., J.S.T., G.R.F., V.G.S., S.R.T., and J.M.P. participated in data acquisition. R.C., E.E.F., T.J.G., and S.M.D. participated in data analysis. All authors contributed to the article preparation.

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DISCLOSURE

Conflict of Interest: J.B.H. is the co-inventor of the Junctional Emergency Treatment Tool (JETT). All other authors report no conflicts of interest. Disclaimer: The opinions or conclusions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of any sponsor.

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EDITORIAL CRITIQUE

Dr. Chang and his team are to be congratulated for a comprehensive review of over 500 patients treated at multiple urban level I trauma centers over 4 years, aimed at precisely describing the specific anatomic locations of non-compressible torso hemorrhage (NCTH) and characterizing the features of the endovascular (ENDO) vs open (OPEN) approach to addressing said injuries. As with any clinical problem, understanding exactly what we are dealing with is the first step to innovating new solutions and refining current ones.

The authors report a decreased mortality in patients with NCTH undergoing ENDO vs OPEN approaches to hemorrhage control. The main limitation related to the reported decrease in

mortality in the ENDO group, as recognized in the article, are the significant differences between the groups being compared. The two groups are arguably not clinically comparable groups obviating the utility of a statistical comparison.

However, the present article is an excellent and detailed description of a wide range of injuries resulting in NCTH and their management. Among several interesting observations, the authors noted a significant increase in the use of ENDO to control hemorrhage over the 4-year timeframe of the study (from 21% up to 41%). Advances in technology such as the hybrid operating room and devices for NCTH control, being developed and employed as early as the pre-hospital setting, (examples that the authors note) are sure to push the use of ENDO even higher in years to come.

The patients included in the present study were managed consistent with current practice recommendations, including the EAST guidelines, advocating for endovascular techniques depending on anatomic location of hemorrhage and patient physiology. Practice guidelines will undoubtedly evolve and be revised, with broadening criteria for injury severity and clinical stability acceptable for endovascular management as the aforementioned technology is refined and studied. I look forward to following the author team's continued work in the field, confident it will be instrumental in the ongoing changes we will see in the care of injured patients who sustain NCTH.

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Too fast, or not fast enough? The FAST exam in patients with non-compressible torso hemorrhage[☆]

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ABSTRACT

Background: Focused assessment with sonography for trauma (FAST) performance metrics are unknown in patients with non-compressible torso hemorrhage (NCTH).

Methods: Retrospective review of a dedicated NCTH database from four level 1 trauma centers (2008–2012). NCTH was defined as (1) named axial torso vessel disruption; (2) AIS chest or abdomen >2 with shock (base deficit <−4) or truncal operation in ≤90 min; or (3) pelvic fracture with ring disruption. Patients were grouped by cavity of hemorrhage source and by shock (SBP ≤90).

Results: 274 patients had a FAST prior to diagnosis of NCTH. FAST was positive in 51% of patients with abdominal/pelvic hemorrhage for a false negative rate (FNR) of 49%. FNR was higher for pelvic (61%) versus abdominal (43%) sources ($p = 0.02$). There was no difference between FAST negative or positive patients for ISS, shock, length of stay, or mortality (all $p = NS$). FNR was not improved among the subgroup of NCTH patients with shock ($p = NS$).

Conclusion: FAST identified abdominal/pelvic hemorrhage in approximately half of NCTH patients, and this was not improved among patients presenting with shock.

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Introduction

Non-compressible torso hemorrhage (NCTH) is now widely recognized as a leading cause of preventable morbidity and mortality in both military and civilian trauma centers.^{1–5} Surgeons assessing patients with suspected NCTH often rely on the focused assessment with sonography for trauma (FAST) as a rapid initial screening test. There are widely varying reports of the accuracy and reliability of the FAST exam. Although the FAST exam is primarily aimed at identifying patients with major abdominal bleeding, the performance metrics of FAST are not well described in a large cohort of patients with NCTH.

The objective of this study was to describe the performance metrics of FAST in a large cohort of patients with NCTH.

Material and methods

Data source

Our group previously compiled a dedicated NCTH database of four level 1 trauma centers from 2008 to 2012.⁶ This database was retrospectively reviewed to identify all patients who had a definitive (positive vs. negative) FAST exam prior to having NCTH identified in the abdominal or pelvic cavity. In keeping with our prior study, NCTH was defined as (1) named axial torso vessel disruption; (2) AIS chest or abdomen >2 with shock (base deficit <−4) or truncal operation in ≤90 min; or (3) pelvic fracture with ring disruption. Variables examined can be seen in Table 1 and Table 2.

Study design and study participants

All patients meeting the above criteria were included for

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Table 1
Results by anatomic cavity of injury.

	Abdomen	Pelvis	p
Total, n	119	71	—
FAST negative, n (%)	51 (43%)	43 (61%)	0.02
Male, n (%)	85 (71%)	52 (73%)	0.79
Blunt mechanism, n (%)	80 (67%)	55 (78%)	0.13
Shock, n (%)	64 (44%)	33 (52%)	0.35
In-hospital death, n (%)	33 (28%)	23 (32%)	0.50
Age, mean	35.7	39.1	0.17
ISS, mean	32.7	30.4	0.27
AIS Chest, mean	2.4	1.9	0.09
AIS Abdomen, mean	4.0	3.3	<0.01
ED initial SBP, mean	100.5	92.2	0.11
LOS, mean	20.5	21.8	0.78

Shock: Initial systolic blood pressure of ≤ 90 mmHg; ISS: Injury Severity Score; AIS: Abbreviated Injury.

Scale; SBP: Systolic Blood Pressure (mmHg); LOS: Length of Stay (days).

Table 2
Results stratified by FAST.

	False Negative	True Positive	p
Total	94	96	—
Abdomen, n (%)	51 (54%)	68 (71%)	0.02
Male, n (%)	67 (71%)	70 (73%)	0.80
Blunt mechanism, n (%)	78 (83%)	57 (59%)	<0.01
Shock, n (%)	42 (49%)	44 (51%)	0.82
In-hospital death, n (%)	25 (27%)	31 (32%)	0.39
Age, mean	40.8	33.2	<0.01
ISS, mean	31.7	31.9	0.94
AIS Chest, mean	2.5	2.0	0.04
AIS Abdomen, mean	3.5	4.0	<0.01
LOS, mean	19.6	22.4	0.54

Shock: Initial systolic blood pressure of ≤ 90 mmHg; ISS: Injury Severity Score; AIS: Abbreviated Injury.

Scale; SBP: Systolic Blood Pressure (mmHg); LOS: Length of Stay (days).

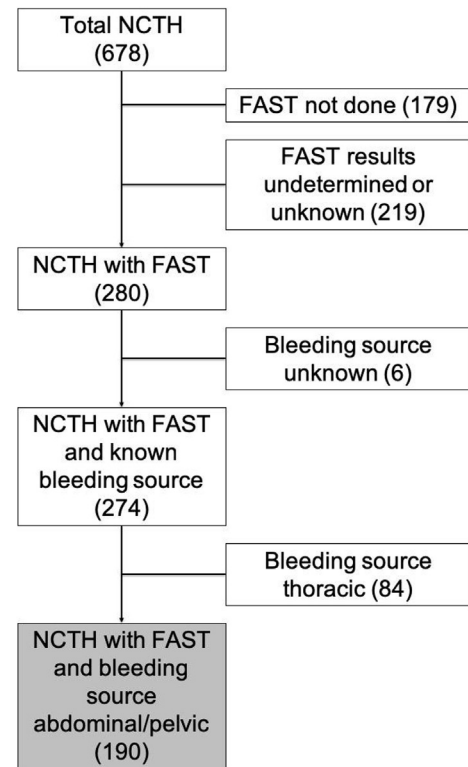
consideration. Patients were excluded if (1) FAST was not performed, (2) FAST results were indeterminate or unknown, (3) primary source of hemorrhage was unknown, or (4) primary source of hemorrhage was identified in the thoracic cavity. Fig. 1 depicts the flow diagram arriving at a final sample of patients with a definitive (positive vs. negative) FAST exam who went on to have NCTH identified in the abdominal or pelvic cavity. Patients were grouped by cavity of hemorrhage source (thoracic vs. abdominal vs. pelvic) and by shock (SBP ≤ 90 mmHg).

Statistical analysis

Intergroup comparisons were performed using Chi-square and Fisher's exact testing for categorical variables. Continuous variables were analyzed with independent samples t-testing and one-way ANOVA. Statistical tests were two-tailed and significance was set at $p < 0.05$. Analysis was performed using SPSS version 21 (IBM; Armonk, NY, USA).

Results

During the 5-year study period, 678 patients with NCTH were identified. Of these, 274 patients underwent FAST examination prior to diagnosis of NCTH. Definitive diagnosis was made by operative exploration (50%), CT angiography (28%), or traditional angiography (19%). The source of NCTH was thoracic in 84 patients, abdominal in 119, and pelvic in 71. The FAST was positive in only 51% of patients with abdominal or pelvic hemorrhage for an overall

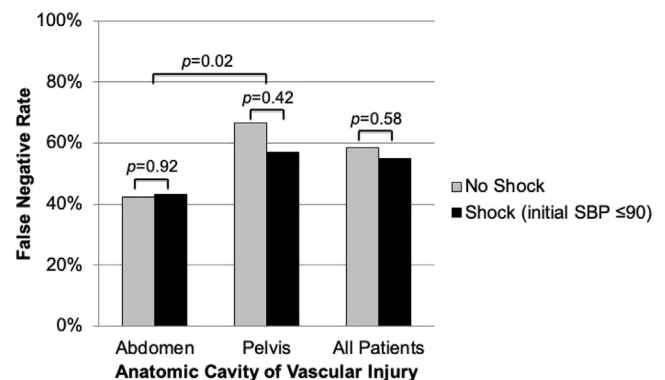
**Fig. 1.** Flow diagram of patient selection. Final sample noted in gray.

false negative rate (FNR) of 49% (sensitivity of 51%). The FNR was significantly higher for pelvic (61%) versus abdominal (43%) sources ($p = 0.02$) (Fig. 2).

There was no difference in age, gender, mechanism of injury, ISS, initial ED SBP, shock at presentation, or in-hospital mortality for patients with an abdominal vs. pelvic source of NCTH (all $p = \text{NS}$) (Table 1).

Furthermore, there was no difference between FAST negative or positive patients for gender, ISS, shock, length of stay, or mortality (all $p = \text{NS}$) (Table 2). However, mechanism of injury was blunt (as opposed to penetrating) in significantly more cases of false negatives (83%) vs. true positives (59%).

FAST performance metrics were not improved among the subgroup of NCTH patients with hemodynamic instability at presentation ($p = \text{NS}$). In addition, the FNR among those requiring laparotomy for hemorrhage control was 41% (abdominal) and 36% (pelvic).

**Fig. 2.** False negative rate by anatomic cavity of vascular injury. Further stratified by shock at initial presentation.

FNR did differ depending on the specific vessel injured (Table 3). Central vessels carried the lowest FNR at 37%, which was significantly lower than perinephric (45%), pelvic (61%), or distal branches (64%) ($p = 0.014$).

Discussion

The objective of this study was to describe the performance metrics of FAST in a large cohort of patients with NCTH. Our key findings were that (1) FAST carried an FNR of 49% and sensitivity of 51%; (2) the FNR was significantly higher for pelvic (61%) versus abdominal (43%) sources of NCTH; (3) FNR was no better in patients with hemodynamic instability at presentation; and (4) FNR among those requiring laparotomy for hemorrhage control was 41% (abdominal) and 36% (pelvic).

Additionally, when we examined the FNR by vessel injured, we found that alarmingly high FNRs could be seen even with major vascular injuries. When central vessels were injured, FNRs were as high as 37%, and this rate only increased with injuries to perinephric vessels (45%), pelvic vessels (61%), or distal branches (64%). This is among the first reports of FNR stratified by specific vessel injury; however, prior studies have demonstrated a lack of correlation between presence of vascular injury and positive FAST, specifically in the setting of blunt trauma.⁷ Still other reports of patients with an initially negative FAST followed by a positive laparotomy have demonstrated high rates of splenic injury requiring splenectomy, liver laceration requiring packing, and mesenteric lacerations requiring repair/resection,⁸ not to mention the potential for missed injuries to the urinary system, diaphragm, adrenals, or any combination of the above.⁹ Given the potential clinical implications of missed hemorrhage, we recommend interpreting a negative FAST exam with caution if NCTH is suspected.

All of the patients in our database were positive for the outcome of interest (NCTH). This meant that each patient with a positive FAST had a “true positive” and each patient with a negative FAST had a “false negative”. Therefore, we were unable to capture false positives or true negatives, without which, we cannot comment on test characteristics such as specificity, positive predictive value, and negative predictive value.

This is the first study in the literature to specifically examine the performance of the FAST exam in the NCTH population. In other populations, numerous studies have highlighted the false negative rate as the key limitation of the FAST exam.^{7,9–32} In adults, studies have generally shown a sensitivity of 80%–88%, specificity of 98%–

100%, positive predictive value of 73%–83%, negative predictive value of 84%–99%, and an accuracy of 97%–99%.^{12–15}

However, these generalized reports of sensitivities in the 80% range (corresponding to an FNR of 20%) may be misleading in certain populations. For example, sensitivities as low as 28% have been reported in patients with pelvic fractures, an important subgroup of the NCTH population.²⁵ Another study found that in patients with splenic injury, sensitivity was as low as 28% if the patient presented with hemodynamic stability but 53% if the patient presented with hemodynamic instability.⁷ Further on the implications of hemodynamic stability, in patients with hypotension at presentation, sensitivities of 79% have been reported.⁸ Additionally, many studies fail to comment on the quandary of the pregnant patient with equivocal or negative FAST exam findings. Collectively, these reports on the limitations of the FAST exam are congruent with our findings.

In the context of the broader literature, we feel that three particular points are salient. First, the original description of the FAST exam by Rozycki et al. suggests that the intent of the exam was for positive FAST exams to guide management, but negative FAST exams (in the setting of high false negative rates) should not dissuade sound clinical judgment.¹³ Second, the FAST exam represents a snapshot of a single point in time, and repeated iterations might become warranted depending on then clinical condition of the patient. Finally, in light of this evidence, institutions may consider prospectively measuring their FAST exam false negative rates as a quality improvement measure to provide feedback to both clinicians and trauma systems.

Limitations

This study carries several notable limitations, largely due to its nature as a retrospective, *post-hoc* analysis of data collected for another study. First, we were bound by the operational definition of NCTH previously established by the NCTH Study Group. On one hand, this was advantageous to maintain consistency between studies and homogeneity of the patient sample. However, this is a research-driven definition of NCTH, and from a practical standpoint, clinicians may not be calculating AIS scores in the preoperative setting or know there is “named axial torso vessel disruption” before they operate.

Second, a sizeable proportion of patients had a FAST that was not done, unknown, or indeterminate. This may be reflective of clinical decision-making that is inherently difficult to capture in a

Table 3
False negative rate by vessel injured.

Injured Vessel	Negative	Positive	Total	False Negative Rate
Central	29	50	79	37%
Abdomen (not otherwise specified)	0	1	1	0%
Portal, hepatic, splenic, superior mesenteric vein	3	6	9	33%
IVC	6	11	17	35%
Celiac, hepatic, splenic, superior mesenteric, inferior mesenteric artery	15	27	42	36%
Aorta	5	5	10	50%
Perinephric	9	11	20	45%
Renal vein	0	3	3	0%
Renal artery	7	7	14	50%
Gonadal vein	2	1	3	67%
Pelvic	42	27	69	61%
Iliac vein	2	8	10	20%
Internal pudendal, obturator, or superior gluteal artery	7	4	11	64%
Iliac artery	33	15	48	69%
Distal Branches	14	8	22	64%

Abbreviations: IVC: inferior vena cava.

Distal branches include (n): inferior epigastric artery (4), mesenteric artery (3), gastropiploic artery (3), lumbar artery (3), phrenic vessels (2), short gastric artery (1), omental artery (1), ovarian vein (1), superior epigastric artery (1), gastroduodenal artery (1), left gastric artery (1), and middle colic artery (1).

database. Nonetheless, this adds to the challenge of drawing generalizable conclusions from this study.

Third, because of the way our data only captured true positives and false negatives, we were unable to capture false positives or true negatives, without which, we cannot comment on specificity, positive predictive value, and negative predictive value.

Fourth, the NCTH database did not capture detail regarding who specifically performed or interpreted the FAST. Operator variability has been cited as a significant source of error, particularly in centers where trainees are performing FAST exams, even if those exam are interpreted by certified professionals.⁷ Bearing in mind that the accuracy of the FAST exam can vary depending on the examiner and the interpreter, we are unable to comment on the impact of this notable variable.

Conclusions

FAST carried a false negative rate as high as 50% in patients with NCTH. This was not significantly improved among NCTH patients presenting with hemodynamic instability. Even when central vessels were injured, false negative rates were as high as 37%, and this rate only increased with injuries to perinephric vessels (45%), pelvic vessels (61%), or distal branches (64%). Given the potential clinical implications of missed hemorrhage, the authors recommend interpreting a negative FAST exam with caution if NCTH is suspected.

Conflicts of interest

The authors have no conflicts of interest or financial disclosures which pertain to this study.

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Disclosure

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APPENDIX 3. Prospective study manuscript

Opportunities for improving times to intervention and hemorrhage control: a multicenter prospective study of noncompressible torso hemorrhage

Abstract

Background: Patients with hemodynamic instability and non-compressible torso hemorrhage (NCTH) are clinically challenging. Endovascular interventions including targeted embolization by interventional radiology (IR) are frequently utilized for hemorrhage control. Hybrid trauma operating rooms and endovascular training for trauma surgeons have been proposed as a means of decreasing times to hemorrhage control. We aimed to determine the most common injuries managed by endovascular intervention in patients with NCTH.

Methods: This is a prospective study of adult trauma patients with NCTH admitted to four urban Level I trauma centers from November 2016-January 2018. Inclusion criteria were age >15 or weight $\geq$ 50 kg, torso hemorrhage requiring endovascular (ENDO) or open (OPEN) intervention or resuscitative thoracotomy (RT) within 240 minutes from ED arrival. Exclusion criteria were prisoners and known pregnancy.

Results: 292 patients with NCTH underwent ENDO (n = 92, 32%), OPEN (n = 179, 61%), or RT (n=21, 7%). ENDO patients had more blunt trauma (90% vs. 44% vs 29 %), and increased times to intervention (median 111 vs. 39 vs. 22 minutes) and hemorrhage control (184 vs. 107 vs. 51 minutes) compared with OPEN and RT. Patients in the ENDO group required fewer blood products than those in the OPEN and RT groups. In-hospital mortality was decreased in the ENDO group compared with OPEN and RT groups (13% vs. 28% vs. 81%). Three vascular and solid organ injuries, consisting of the spleen, internal iliac arteries, and liver, accounted for 61% of all ENDO interventions, while OPEN and RT injuries were more varied.

Conclusions: Patients undergoing endovascular intervention for NCTH experience longer time to intervention and definitive hemorrhage control. Given the narrow injury pattern, consideration should be given to increased endovascular training for trauma surgeons in order to improve treatment times and outcomes.

Introduction

Noncompressible torso hemorrhage, secondary to both blunt and penetrating injuries, is highly lethal (1-4). In comparison to peripheral or junctional vascular injuries, thoracic and abdominal vascular injuries are not amenable to hemorrhage control with tourniquets or compression, making patients with NCTH and hemodynamic instability clinically challenging. (2, 5) NCTH is increasingly being managed with endovascular interventions including targeted embolization by interventional radiology (IR). (6-12)

Prior studies have demonstrated endovascular control techniques improve survival and decrease exsanguination and complications compared to traditional open vascular surgical techniques in NCTH patients. (11, 13) However, treatment delays may occur for patients injured during the off-hours (i.e. nights and weekends) when interventional radiologists are not typically on call in the hospital.(14) Trauma hybrid operating rooms (THOR) and increased endovascular training for trauma surgeons have been proposed as a means of addressing these treatment delays and decreasing times to intervention and hemorrhage control. (15-18) In order to implement training which effectively teaches trauma surgeons the endovascular skills necessary to manage NCTH patients, it is imperative to understand the injury patterns among this patient population.

The main objective of this study was to identify and document the specific location, size and name of all vessels or organs requiring hemorrhage control among patients with NCTH in order to define specific vascular and solid organ injuries that are amenable to endovascular repair and management techniques.

Patients and Methods

Study Setting

Approval for this study was obtained from institutional review boards at each of the four participating institutions (University of Texas Health Science Center at Houston, Baylor College of Medicine, the University of Texas Health Science Center at San Antonio, and the San Antonio Military Medical Center, as well as the Human Research Protections Office of the US Army Medical Research and Material Command). These hospitals comprise all of the level 1 trauma centers in the Houston and San Antonio metropolitan areas.

Study Design

We conducted a prospective observational study involving patients with NCTH. Adult patients (>15 years of age or ≥ 50 kg body weight if age unknown) undergoing a truncal procedure (endovascular or open) within 4 hours of emergency department (ED) arrival between November 2016 to January 2018, were included. Prisoners and those with known pregnancy were excluded. A waiver of informed consent was obtained given minimal risk to patients. The Strengthening of the Reporting of Observational Studies in Epidemiology guidelines for observational studies were followed. (19)

Clinical research staff, available on a 24/7 basis at the participating centers, were responsible for screening and collecting data on all highest activation trauma patients meeting inclusion criteria upon arrival to the ED. Direct observation was continued until the truncal procedure was completed and the patient arrived at a nursing unit, the patient expired, or no surgical or endovascular procedures were initiated within 4 hours of ED arrival. All patient care

utilized the participating center's standards, policies and procedures. No study interventions, drugs, or devices were assigned to subjects.

Definition and Outcomes

Direct data collection included prehospital information (times, injury details, life-saving interventions [LSIs], fluid and blood product usage, and vital signs) and inpatient information (vital signs, LSIs, fluid and blood product usage, routine laboratory results, diagnostic procedures, interventional procedures, hemorrhage control devices, and time to hemostasis). Radiological and operative reports were reviewed in order to accurately localized specific vascular or solid organ injuries.

Patients were divided into three groups based on the initial approach to hemorrhage control: OPEN (without resuscitative thoracotomy), endovascular ([ENDO], including REBOA), and resuscitative thoracotomy (RT). Patients who underwent both ENDO and OPEN interventions for initial hemorrhage control, were assigned to the OPEN group, which is the more invasive intervention. Study data were collected and managed using Research Electronic Data Capture (REDCap) hosted at UT Health. REDCap is a secure, web-based application designed to support data capture for research studies.(20, 21)

Statistical Analysis

All statistical analyses were completed using R version 3.53 (R Core Team. 2013. R: A language and environment for statistical computing. R Foundation for Statistical Computing). Continuous variables were reported as medians and interquartile ranges (IQRs). Chi-square, Fisher's, and Wilcoxon rank-sum and Kruskal-Wallis tests were used to compare categorical, sparse categorical and continuous variables, respectively

Results

Demographics

Over the 14-month study period, 319 patients were observed. Twenty-seven patients were excluded: 24 who had no truncal hemorrhage and 3 who underwent truncal procedure greater than 4 hours after ED arrival. A total of 179 patients (61%) underwent OPEN intervention, 92 patients (32%) underwent ENDO intervention, and 21 patients (7%) underwent RT. A total of 24 patients in the OPEN (13%) and 12 patients (13%) in the ENDO group underwent REBOA.

Demographics and admission parameters are summarized in **Table 1**. Patients in the ENDO group were older and had higher incidence of blunt trauma than OPEN and RT patients. Patients undergoing ENDO had higher base excess on arrival than those in the OPEN and RT groups. Arrival systolic blood pressure, hemoglobin, and platelet counts were similar in the ENDO and OPEN groups, but significantly higher compared to those requiring RT.

Procedural Information and Time to Intervention

Procedural information is summarized in **Table 2**. ENDO patients had significantly longer times to intervention and hemorrhage control compared to OPEN and RT patients. The majority of patients in the ENDO group had their initial procedure performed by interventional radiology as compared to the OPEN and RT groups which were predominately performed by trauma surgeons.

Blood Product Transfusions and Mortality

Outcomes data are summarized in **Table 3**. ENDO patients received fewer RBCs, plasma, and platelets within 24-hours of arrival compared to patients in the OPEN and RT

groups. ENDO patients experienced a greater number of hospital-free days and ICU-free days compared with patients in the OPEN and RT groups. Across all groups, thirty-day in-hospital mortality was 22.9%, with significantly lower rates in the ENDO group compared with OPEN and RT groups. Among patients who did die, time to death was significantly longer in the ENDO group compared with OPEN and RT.

The most common cause of death among all patients was exsanguination (64%), with a median time to death in these patients of 3.1 hours (IQR 1.4-13.2). Exsanguination was a significantly less frequent cause of death in the ENDO group compared to the OPEN and RT groups.

Description of Vascular Injury

Vascular and solid organ injury locations are summarized in **Table 4**. The majority of vascular injuries in the ENDO group were in the pelvis, compared with a majority of vascular injuries in the abdomen in the OPEN and RT groups. All groups experienced large percentages of solid organ injuries (48.9% ENDO vs 61% OPEN vs 57% RT). In the ENDO group, three anatomic locations--the spleen (n=30, 32.6%), internal iliac arteries (n=16, 17.6%), and liver (n=10, 10.9%) -- accounted for 61% of all endovascular interventions performed, while the vascular injuries in the OPEN and RT groups were much more varied. In the OPEN group, 22 patients underwent intervention for venous injuries, in contrast with just two venous injuries in each of the ENDO and RT groups.

Endovascular Outcomes by Specialty

Among patients undergoing ENDO, the majority were performed by Interventional Radiology (IR), (n=62, 67%). Time to intervention was significantly shorter in those ENDO

procedures performed by trauma surgery as compared to those performed by IR (median, 111 minutes vs. 36 minutes, $p<0.001$). ENDO patients whose procedure was performed by a trauma surgeon were transfused significantly more platelets (1 vs 0, $p<0.001$) and plasma (5 vs 0, $p<0.001$), but no difference in RBCs than those who procedure was performed by IR. The most common injuries were similar among those treated by IR and trauma surgery, with splenic, internal iliac artery and liver injuries comprising the majority.

Discussion

The current study demonstrated that patients undergoing endovascular intervention had a relatively narrow injury pattern compared to patients undergoing open intervention or RT as well as significantly increased times to intervention and hemorrhage control. Sixty-one percent of all injuries treated by endovascular intervention were comprised of just three injuries—the spleen, internal iliac arteries, and the liver. In a previously published retrospective review of patients at the same four institutions, the majority of ENDO patients underwent intervention for injuries to the descending thoracic aortic and internal iliac arteries. Due to nearly all descending thoracic aortic procedures being performed by vascular surgery in a non-emergent fashion, these patients were excluded from this prospective study due to the procedure taking place >240 minutes after ED arrival, thus accounting for the differences in injury patterns observed here. In addition, the retrospective study did not include information regarding solid organ injuries. (13)

Previous studies have demonstrated delay to IR in hemodynamically unstable patients is independently associated with a two-fold increase in mortality risk.(6, 12) Our data on patients with NCTH emphasize the necessity of decreasing times to intervention and improving times to hemorrhage control in order to improve overall patient outcomes. Management of NCTH patients is frequently complicated by need for intrahospital transport to each diagnostic and

therapeutic intervention as well as variation in specialist availability depending on the day and time of injury.(15) Multiple groups have advocated for increased utilization of THORs with capabilities to perform open and endovascular diagnostic and interventional procedures in addition to increased endovascular training opportunities for trauma surgeons. (22) From a patient care perspective, THORs serve as a place where all necessary procedures including CT scans, endovascular interventions, and operations can occur, thus maintaining a multidisciplinary team approach and minimizing patient transport.(15, 16) While consolidating diagnostic and therapeutic procedures to a single location will undoubtedly decrease intrahospital travel times, it does not address delays to intervention caused by lack of specialist availability, especially in the off-hours.

To this end, adoption of endovascular intervention by trauma surgeons, is a potential solution to further decreasing treatment delay and times to intervention and hemorrhage control. From a technical standpoint, trauma and acute care surgeons already have the basic wire and catheter skills required to perform endovascular procedures as obtaining arterial and venous access and the use of fluoroscopy to determine device placement and delineate anatomy are standard practice in management of critically-ill patients. In addition, more recent graduates of surgical training programs, have formal endovascular experience as these procedures have become commonplace in the field of vascular surgery. Studies evaluating endovascular skills training for trauma surgeons utilizing virtual reality as well as live animal simulations have demonstrated rapid attainment of proficiency in basic endovascular skills independent of endovascular experience or years since residency training. In addition to REBOA, a recent study of the Endovascular Skills for Trauma and Resuscitative Surgery (ESTARS) course demonstrated effectiveness at teaching selective angiogram, embolization, and stent placement for diagnosis

and control of hemorrhage. (17, 18) Given the demonstrated effectiveness of these courses and the relatively narrow injury pattern of patients with NCTH amenable to endovascular therapies, one can conclude that it is feasible to develop a curriculum to train trauma and acute care surgeons to perform procedure which address the most common injuries.

Limitations of this study include confounding by indication bias. Despite ENDO patients having longer times to intervention and hemorrhage control, they experienced decreased mortality and exsanguination, and more hospital-free and ICU-free days than their OPEN and RT counterparts. These superior outcomes, in addition to having lower rates of hypotension and shock on arrival, indicate that ENDO patients were overall more stable, and thus physiologically able to tolerate longer wait times in order to undergo endovascular intervention.

Conclusion

Patients undergoing endovascular intervention for NCTH experience longer time to intervention and definitive hemorrhage control. Given the narrow injury pattern amongst patients undergoing endovascular intervention, consideration should be given to increased endovascular training for trauma surgeons in order to improve treatment times and patient outcomes.

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Table 1. Demographics and Admission Parameters				
	ENDO (n=92)	OPEN (n=179)	RT (n=21)	<i>p</i>
Age	38 (27-57)	32 (23-49)	33 (24-43)	0.07
Male	67 (73%)	152 (85%)	17 (81%)	0.06
Blunt	83 (90%)	82 (46%)	6 (29%)	<0.001
ED SBP	105 (87-128)	102 (85-123)	70 (50-93)	<0.001
ISS	26 (17-38)	26 (17-37)	34 (25-41)	0.34
ED GCS	15 (9-15)	14 (3-15)	3 (3-6)	<0.001
ED GCS Motor	6 (5-6)	6 (1-6)	1 (1-1)	<0.001
ED base excess, mEq/L	-4 (-7, -2)	-6 (-10, -3)	-16 (-20, -11)	<0.001
ED Hemoglobin	12.6 (11.0-14.0)	12.4 (10.87-13.5)	10.9 (9.1-12.7)	0.03
ED Platelet count (x10 ⁹ /L)	218 (167-252)	215 (157-265)	100 (90-166)	<0.001
Life-saving interventions in ED				
Aortic clamping	0 (0%)	0 (0%)	12 (57%)	<0.001
CPR	1 (1%)	6 (3.3%)	12 (57%)	<0.001
ED thoracotomy	0 (0%)	0 (0%)	21 (100%)	<0.001
Pelvic binder	9 (10%)	3 (1.7%)	0 (0%)	0.01
REBOA	12 (13%)	24 (13.4%)	0 (0%)	0.20

ED, emergency department; GCS, Glasgow Coma Scale; AIS, Abbreviated Injury Scale; Hgb, hemoglobin
 *SBP, <90 mgHg
 **Base excess, <-4 mEq/L
 Continuous data presented as median (IQR)

Table 2. Procedural Information				
	ENDO (n=92)	OPEN (n=179)	RT (n=21)	p
Time to Intervention (min)	111 (81-159)	41 (29-64)	22 (8-31)	<0.001
Time to hemorrhage control (min)	184 (147-242)	107 (70-164)	51 (24-76)	<0.001
Number of patients achieving hemorrhage control	83 (90%)	156 (87%)	5 (24%)	0.07
Time to resuscitation complete (min)	186 (146-254)	125 (69-190)	126 (76-260)	<0.001
Type of Surgeon at Initial Intervention				
Trauma	12 (13%)	176 (98%)	21 (100%)	<0.001
Vascular	14 (15%)	2 (1%)	0	
Thoracic	4 (4%)	0 (0%)	0	
IR	62 (67%)	0 (0%)	0	
Location at Initial Intervention				
ED	5 (5%)	2 (1%)	11 (52%)	<0.001
IR	32 (35%)	0 (0%)	0 (0%)	
OR	5 (4%)	163 (91%)	5 (24%)	
Hybrid OR	50 (54%)	14 (8%)	5 (24%)	
ED, emergency department; IR, interventional radiology				
Continuous data presented as median (IQR)				

Table 3. Outcomes				
	ENDO (n=92)	OPEN (n=179)	RT (n=21)	p
Number of patients transfused	61 (66%)	151 (84%)#	21 (100%)	<0.001
24h RBC transfused (units)	3 (0-7)	5 (2-13)	20 (13-33)	<0.001
24h Plasma transfused (units)	2 (0-6)	5 (0-11)	16 (4-34)	<0.001
24h Platelets transfused (units)	0 (0-6)	6 (0-12)	12 (6-24)	<0.001
Rebleeding	10 (11%)	3 (2%)	1 (5%)	0.003
ICU-free days	23 (16-25)	22 (13-25)	0 (0-0)	<0.001
Hospital-free days	16 (3-21)	14 (0-21)	0 (0-0)	<0.001
Death	12 (13%)	38 (21%)	17 (81%)	<0.001
Causes of Death*				
Exsanguination	3 (25%)	24 (63%)	16 (94%)	<0.001
TBI	7 (58%)	14 (37%)	1 (6%)	1
Respiratory	1 (8%)	6 (16%)	3 (18%)	0.03
Sepsis/MOF	2 (16%)	8 (21%)	2 (12%)	0.22
MI/stroke	5 (42%)	11 (29%)	4 (25%)	0.10
Pulmonary embolus	0 (0%)	2 (5%)	0 (0%)	0.24
Time to death, hours	34 (3-113)	23 (3-159)	1.5 (1.1-3.0)	<0.001
RBC, red blood cells; MOF, multiple organ failure; MI, myocardial infarction				
* Not mutually exclusive.				
Continuous data presented as median (IQR)				

Table 4: Anatomic Location of Vascular and Solid Organ Injury		
	ENDO (n=92, 32%)	OPEN (n=200, 68%)
Chest	12 (13.0%)	20 (10%)
Pulmonary artery		3 (1.5%)
Heart		4 (2%)
Ascending aorta	1 (1.1%)	1 (0.5%)
Right subclavian/axillary artery	2 (2.2%)	
Intrathoracic common carotid arteries		2 (1%)
Left subclavian artery	1 (1.1%)	1 (0.5%)
Intercostal/internal thoracic arteries	3 (3.3%)	2 (1%)
Descending thoracic aorta	3 (3.3%)	1 (0.5%)
Right superior phrenic artery	1 (1.1%)	
Intrathoracic internal/external jugular veins		2 (1%)
Inferior vena cava		3 (1.5%)
Chest unknown	1 (1.1%)	1 (0.5%)
Abdomen	11 (12%)	40 (20%)
Abdominal aorta		1 (0.5%)
Left hepatic artery	1 (1.1%)	
Right hepatic artery		1 (0.5%)
Right gastric artery		1 (0.5%)
Splenic artery	7 (7.7%)	
Left gastric artery		2 (1%)
Superior mesenteric artery		4 (2%)
Inferior mesenteric artery		5 (2.6%)
Renal arteries	3 (3.3%)	1 (0.5%)
Infrarenal aorta		3 (1.5%)
Gonadal arteries		2 (1%)
Left renal vein		3 (1%)
Gonadal veins		2 (1%)
Portal vein		1 (0.5%)
Superior mesenteric vein		3 (1.5%)
Inferior mesenteric vein		3 (1.5%)

Abdomen unknown		9 (4.6%)
Pelvis	24 (26.4%)	17 (8.5%)
External iliac arteries	1 (1.1%)	1 (0.5%)
Inferior epigastric arteries		4 (2%)
Other external iliac artery branches	1 (1.1%)	
Internal iliac arteries	16 (17.6%)	3 (1.5%)
Internal iliac artery branches	4 (4.4%)	
Common iliac veins		5 (2.6%)
External iliac veins		2 (1%)
Internal iliac veins	1 (1.1%)	1 (0.5%)
Pelvis unknown	1 (1.1%)	1 (0.5%)
Solid Organ Injury	45 (48.9%)	122 (61%)
Lung		11 (5.5%)
Liver	10 (10.9%)	52 (26%)
Spleen	30 (32.6%)	49 (24.5%)
Kidney	5 (5.4%)	10 (5%)

Endovascular Intervention Outcomes by Physician Type

	IR (n=62)	Trauma Surgery (n=12)	p
Time to Intervention (min)	111 (88-155)	36 (11-79)	<0.001
Time to Hemorrhage Control (min)	191 (158-238)	114 (111-137)	<0.001
24 hour RBC (units)	2 (0-6)	6 (5-9)	0.37
24 hour Platelets (units)	0 (0-1)	1 (0-1)	<0.001
24 hour Plasma (units)	0 (0-0)	5 (0-7)	<0.001
Injuries:			
Spleen	23 (37%)	4 (33%)	0.39
Internal iliac aa.	11 (18%)	2 (17%)	
Liver	6 (10%)	2 (17%)	
Splenic artery	6 (10%)	0 (0%)	
Death	6 (9.7%)	6 (50%)	0.003
Time to death	54 (32-82)	4 (2-148)	0.004

	IR (n=62, 67%)	Trauma/Vascular/Thoracic Surgeons (n=30)	p
Time to Intervention (min)	111 (88-155)	106 (65-162)	<0.001
Time to Hemorrhage Control (min)	191 (158-238)	153 (117-230)	<0.001
24 hour RBC (units)	2 (0-6)	5 (0-7)	<0.001
24 hour Platelets (units)	0 (0-1)	1 (0-4)	0.84
24 hour Plasma (units)	0 (0-0)	6 (1-15)	0.07
Injuries:			
Spleen	23 (37%)	15 (33%)	
Internal iliac aa.	11 (18%)	6 ()	
Liver	6 (10%)	11 (17%)	
Splenic artery	6 (10%)	1	
Death	6 (9.7%)	6 (20%)	0.20
Time to death	54 (32-82)	5 (2-149)	<0.001