AWARD NUMBER: W81XWH-16-2-0012

TITLE: Aortic Hemostasis and Resuscitation Advanced REBOA for NCTH and Reversal of HiTCA

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REPORT DATE: Oct 2019

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
Oct 2019	Final	15 May 2016 - 31 JUL 2019

4. TITLE AND SUBTITLE

Aortic Hemostasis and Resuscitation Advanced REBOA for NCTH and Reversal of HiTCA

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-16-2-0012

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The majority of combat and civilian casualties are due to severe uncontrolled, non-compressible hemorrhage resulting in cardiovascular collapse. Current resuscitation techniques, including cardiopulmonary resuscitation (CPR), thoracotomy, and aortic cross-clamping to reverse hemorrhage-induced traumatic cardiac arrest (HiTCA), are very invasive and ineffective for austere combat casualties. Aortic Hemostasis and Resuscitation (AHR) is advanced form of resuscitative endovascular balloon occlusion of the aorta (REBOA) that has been recently shown to promote return of spontaneous circulation (ROSC). This study examines the survival benefit of AHR in otherwise fatal non-compressible torso hemorrhage (NCTH) with HiTCA. It aims to compare the efficacy of the selective aortic arch perfusion (SAAP) catheter when used with fresh whole blood or an oxygen therapeutic (HBOC). In addition, it aims to demonstrate the feasibility of the conversion from SAAP therapy to limited extra-corporeal life support (ECLS), and also to determine the impact of ECLS on critical physiology. To do this, we utilized a model of swine NCTH and HiTCA in a series of experiments in which each animal underwent a liver laceration and allowed to free bleed for five minutes through the SAAP catheter to achieve HiTCA. Then, resuscitation fluid is selectively perfused through the balloon catheter to the heart and brain, while also limiting non-compressible bleeding below the balloon. As a result, ROSC was achieved in 100% of the FWB animals and 86% of the HBOC-201 animals (p=0.12). Overall survival (t = 320 min) was 92% in the FWB group and 67% in the HBOC-201 group (p=0.12). This study shows that the SAAP catheter is an effective method of hemorrhage control by promoting ROSC and sustaining life in pre-hospital transport. AHR promotes hemodynamic stability and has the potential to fill a critical unmet gap in military and civilian trauma care.

15. SUBJECT TERMS
Non-compressible torso hemorrhage (NCTH), hemorrhage-induced traumatic cardiac arrest (HiTCA), resuscitative endovascular balloon occlusion of the aorta (REBOA), aortic hemostasis and resuscitation (AHR), hemoglobin-based oxygen carrier (HBOC), selective aortic arch perfusion (SAAP), extracorporeal life support (ECLS), extracorporeal membrane oxygenation (ECMO)

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	130	19b. TELEPHONE NUMBER *(include area code)*

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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope

Uncontrolled, non-compressible hemorrhage resulting in cardiovascular collapse accounts for the majority of civilian and military casualties. Current techniques used against hemorrhage-induced cardiac arrest in severe combat casualty care have been shown to be ineffective, thus survival rates are low. In contrast, aortic hemostasis and resuscitation (AHR) has been shown to be effective in hemorrhage control. AHR with oxygenated whole blood and packed red blood cells has been shown to stimulate the return of spontaneous circulation (ROSC). SAAP is a technique in which a balloon catheter is introduced into the aorta and inflated to stop bleeding. This study aims to evaluate the effectiveness of selective aortic arch perfusion (SAAP) when used in combination with an external pump system that infuses either fresh whole blood or hemoglobin-based oxygen carrier (HBOC) to provide the body with oxygen after circulation is restored. The main objective is to demonstrate the survival benefit of AHR using a large animal model by effectively achieving ROSC, providing hemodynamic support, and increase pre-hospital transport and long-term survival.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Non-compressible torso hemorrhage (NCTH), hemorrhage-induced traumatic cardiac arrest (HiTCA), resuscitative endovascular balloon occlusion of the aorta (REBOA), aortic hemostasis and resuscitation (AHR), hemoglobin-based oxygen carrier (HBOC), selective aortic arch perfusion (SAAP), extracorporeal life support (ECLS)

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Major Task 1/Phase I (Y1)
Subtask 1: Submit documents for IACUC approval
Milestone # 1 IACUC approval obtained (3/16/2016)
Subtask 2: Submit documents for ACURO approval
Milestone # 2 ACURO approval obtained (10/24/2016)
Subtask 3: Staff Hiring (Q2)
Subtask 4: Surgical capability Start-up including 6 pilot/model refinement animals
Subtask 5: Phase I study execution (two experimental groups): animal experiments – fresh whole SAAP vs HBOC SAAP with critical care observation and limited ECLS as per protocol 24 with schedule for up to 4 technical failures experimental swine total (2 pig per 1-2 weeks); 60 donor swine (Completed 5/5/2017)
Subtask 6: QA of data entry, statistical analysis, and final study report (Completed 7/13/2018)

Major Task 2/Phase II (Y2)
Subtask 1: Development of didactic training component and recruit first class of five participants. (Completed)
Subtask 2: Complete first AHR course. Assess and refine coursework. 3 swine for training. (Completed 05/21-05/22/2019)
Subtask 3: Recruit second class of five participants and complete second AHR course. (Completed 07/10-07/11/2019)
Subtask 4: QA of data entry, statistical analysis, and final study report. (In progress)

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in this section should shift from reporting activities to reporting accomplishments.

1) Phase I experiments and data analysis have been completed in preparation of Y2/Phase II of training development. Y2/Phase II didactic training component has been completed (found in the appendix), along with recruiting and completion of the first and second AHR course.

2) The objectives were to compare the efficacy of SAAP therapy between oxygenated HBOC and oxygenated FWB, and also to determine if SAAP can be converted to SAAP-ECMO therapy without negatively impacting critical physiology achieved by the aortic balloon occlusion.
In this study, the SAAP catheter is introduced into the aorta and inflated to stop bleeding while allowing the administration of oxygenated resuscitation from an external pump system directly into the heart during cardiac arrest to achieve ROSC.

3) The results show that HBOC-201 and fresh whole blood are both effective at promoting ROSC in HiTCA and that the conversion from SAAP to ECMO via the SAAP catheter is feasible.
All FWB animals achieved ROSC, while 12 of the 14 HBOC animals achieved ROSC. Five animals (4 HBOC, 1 FWB) died before the end of experiment. All animals except one that achieved ROSC survived pre-hospital and converted to ECLS. A full manuscript of results are included in the appendix of this document. This manuscript was published in the Journal of Trauma.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Level I/II/III emergency care and trauma providers will be trained in the AHR technique in Y2 to demonstrate its military applicability and survival benefit prior to clinical use.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

An abstract from the Phase I data has been accepted as an oral presentation at the annual meeting for the American Association for the Surgery of Trauma. It was presented on 9/27/2018. A manuscript of Phase I was published in Journal of Trauma on 04/18/2019. A secondary manuscript is in progress describing the physiologic sequalae of the injury complex.

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

If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Recruit participants, and train the emergency providers in the technique to demonstrate its feasibility in a third course. The training will be a combination of didactic lectures, vascular access training, and labs, using a non-recovered swine model of NCTH and HiTCA. Additionally, complete the secondary impacts of the intervention.

4. IMPACT: Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

The aim is for the results to demonstrate that AHR improves ROSC and survival of patients in pre-hospital transport, and ultimately in long-term survival. This likely could change the standard of hemorrhage control and resuscitation strategies. In addition, HBOC has a longer shelf-life than fresh whole blood and may be a future alternative for human erythrocytes. It can be kept at room temperature for up to three years, does not have to be matched with blood type, and can be used on patients with immune systems that attack red blood cells. HBOC could potentially eliminate the need for whole blood in the use of SAAP technology, extending its pre-hospital viability in combat theaters of operation.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Primary impact is the potential adoption of a new resuscitation technique in military and civilian care. Results, use and training algorithms, and new practices will be transferred to both civilian and military centers through training programs and involvement of both civilian and military medical centers in upcoming clinical trials.

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

SAAP and AHR have been shown to increase the likelihood of achieving ROSC, thus survival rates of patients will likely increase, which will decrease the number of fatalities after non-compressible torso hemorrhage (NCTH) and hemorrhage induced traumatic cardiac arrest (HiTCA).

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Nothing to Report.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to Report

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

An IRB waiver was completed on March 26, 2018.

Significant changes in use or care of vertebrate animals.

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

American Association for the Surgery of Trauma Annual Meeting abstract submission March 1, 2018. Manuscript submitted to Journal of Trauma and accepted 04/18/2019.

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report

  Other publications, conference papers, and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Presented at Baylor University Medical Center's Grand Rounds in Dallas May 11, 2017

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to Report

- *Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.*

The primary product is the AHR/SAAP catheter technique which uses an oxygenated fluid to achieve ROSC in order to sustain post-ROSC survival until vascular control of hemorrhage occurs to promote overall long-term survival. SAAP technology is owned by the University of North Carolina and by Resuscitech INC. Resuscitech INC is in the process of manufacturing and pre-FDA submission for SAAP catheters. Use of the SAAP technique in HiTCA will be shared via the training program developed in the second year of this project in addition to worldwide speaking engagements and clinical trials.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *biospecimen collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

The primary reportable outcome of the first phase of this project is an enhanced understanding of the following: 1) use of non-blood product substrates with SAAP perfusion and 2) technical feasibility of transition from SAAP to SAAP-ECLS for cardiac support during critical care.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project? *Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project*

during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort).

Name: James D Ross, PhD
Project Role: PI
Research Identifier: NA
Nearest Person Month Worked: 3
Contribution to Project: ACURO documentation preparation and submission. Pilot experiment execution. Pilot data evaluation. Report preparation. Control administration of blood products. Monitor animals during experiments. Full study execution including surgical procedures, ECMO circuit/pump management and critical care decision making.

Name: James Manning, MD
Project Role:
Research Identifier: NA
Nearest Person Month Worked: 4
Contribution to Project: Developer of SAAP catheter. Monitor animals during experiment. Critical care decision making. Analysis of data and outcomes.

Name: Todd Graham
Project Role: Laboratory Manager
Research Identifier: NA
Nearest Person Month Worked: 9
Contribution to Project: Laboratory equipment set-up and maintenance. Coordination of equipment training protocols. Development of BIOPAC data acquisition templates. Development of consumable supply ordering schedules for phase I. Execution of laboratory experiments. Coordination of data review. DEA licensure coordination and schedule drug ordering.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to Report

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.
Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

The project included a subaward collaboration with the Co-PI, Dr. James Manning, and his laboratory at University of North Carolina as detailed in the contract subaward. All experiments were performed on-site at Oregon Health and Science University.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

Selective aortic arch perfusion with fresh whole blood or HBOC-201 reverses hemorrhage-induced traumatic cardiac arrest in a lethal model of noncompressible torso hemorrhage

Heather E. Hoops, MD, James E. Manning, MD, Todd L. Graham, BS, Belinda H. McCully, PhD, Shane L. McCurdy, BS, *and* **James D. Ross, PhD**, *Portland, Oregon*

BACKGROUND: Hemorrhage-induced traumatic cardiac arrest (HiTCA) has a dismal survival rate. Previous studies demonstrated selective aortic arch perfusion (SAAP) with fresh whole blood (FWB) improved the rate of return of spontaneous circulation (ROSC) after HiTCA, compared with resuscitative endovascular balloon occlusion of the aorta and cardiopulmonary resuscitation (CPR). Hemoglobin-based oxygen carriers, such as hemoglobin-based oxygen carrier (HBOC)-201, may alleviate the logistical constraints of using FWB in a prehospital setting. It is unknown whether SAAP with HBOC-201 is equivalent in efficacy to FWB, whether conversion from SAAP to extracorporeal life support (ECLS) is feasible, and whether physiologic derangement post-SAAP therapy is reversible.

METHODS: Twenty-six swine (79 ± 4 kg) were anesthetized and underwent HiTCA which was induced via liver injury and controlled hemorrhage. Following arrest, swine were randomly allocated to resuscitation using SAAP with FWB (n = 12) or HBOC-201 (n = 14). After SAAP was initiated, animals were monitored for a 20-minute prehospital period prior to a 40-minute damage control surgery and resuscitation phase, followed by 260 minutes of critical care. Primary outcomes included rate of ROSC, survival, conversion to ECLS, and correction of physiology.

RESULTS: Baseline physiologic measurements were similar between groups. ROSC was achieved in 100% of the FWB animals and 86% of the HBOC-201 animals ($p = 0.483$). Survival ($t = 320$ minutes) was 92% (11/12) in the FWB group and 67% (8/12) in the HBOC-201 group ($p = 0.120$). Conversion to ECLS was successful in 100% of both groups. Lactate peaked at 80 minutes in both groups, and significantly improved by the end of the experiment in the HBOC-201 group ($p = 0.001$) but not in the FWB group ($p = 0.104$). There was no significant difference in peak or end lactate between groups.

CONCLUSION: Selective aortic arch perfusion is effective in eliciting ROSC after HiTCA in a swine model, using either FWB or HBOC-201. Transition from SAAP to ECLS after definitive hemorrhage control is feasible, resulting in high overall survival and improvement in lactic acidosis over the study period. (*J Trauma Acute Care Surg.* 2019;87: 263–273. Copyright © 2019 American Association for the Surgery of Trauma.)

KEY WORDS: Resuscitation; traumatic cardiac arrest; *Sus scrofa*; selective aortic arch perfusion.

Hemorrhage is the leading cause of preventable traumatic death in both military and civilian settings, with most deaths occurring prior to medical treatment facility arrival.[1–4] Hemorrhage-induced traumatic cardiac arrest (HiTCA) represents the most severe state of hemorrhagic shock, with a dismal survival rate of 0% to 20% despite current treatment methods (closed-chest compressions, resuscitative thoracotomy, and concurrent blood product resuscitation).[5–7] Using resuscitative endovascular balloon occlusion of the aorta (REBOA) to achieve aortic hemostasis has not improved survival rates in HiTCA[8] and may increase mortality.[9] More efficacious treatment options for HiTCA are needed.

Selective aortic arch perfusion (SAAP) is a novel endovascular aortic occlusion technique that provides the same hemostatic effects as REBOA, but can additionally provide intra-aortic perfusion of the brain and coronary arteries for treatment of HiTCA.[10] While REBOA is effective at treating severe hemorrhagic shock in both a swine model and in clinical settings,[8,11–16] its efficacy in HiTCA is limited.[8,17] Previous studies demonstrated that SAAP using oxygen-carrying perfusates are more effective than SAAP with Lactated Ringer's,[17,18] REBOA[17] and closed-chest compressions (unpublished data) with whole blood resuscitation for reversing HiTCA in a swine model.

Blind placement of intra-arterial catheters in patients with cardiac arrest in a prehospital setting has been shown to be feasible.[8,19–21] However, the logistics of using SAAP with fresh whole blood (FWB) presents a challenge in the prehospital environment due to storage considerations and citrate-related calcium sequestration, requiring coadministration of exogenous calcium.[22]

While controversial in use associated with elective surgery,[23–25] and presently not FDA-approved, the benefits of hemoglobin-based oxygen carrier (HBOC)-201 (HbO_2 Therapeutics, Souderton, PA) and other hemoglobin-based oxygen carriers may outweigh risks in settings where blood products are unavailable or

Submitted: August 1, 2018, Revised: February 27, 2019, Accepted: March 16, 2019, Published online: April 18, 2019.

From the Department of Surgery (H.E.H.), Oregon Health and Science University, Portland, Oregon; Department of Emergency Medicine (J.E.M., S.L.M.), University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; and Division of Trauma, Critical Care and Acute Care Surgery (T.L.G., B.H.M., J.D.R.), Oregon Health and Science University, Portland, Oregon.

Presented at the 77th Annual Meeting at American Association for the Surgery of Trauma, September 26–29, 2018, in San Diego, CA.

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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DOI: 10.1097/TA.0000000000002315

unacceptable due to austere medical environments or religious preferences.[26,27]

Selective aortic arch perfusion using HBOC-201 has been shown to effectively achieve return of spontaneous circulation (ROSC) after HiTCA in a swine model.[18] HBOC-201 may provide additional benefit in the treatment of HiTCA in austere environments or emergent settings as it does not require calcium co-administration. However, there have been no previous randomized trials comparing the efficacy of SAAP with FWB to HBOC-201 in the treatment of HiTCA.

After ROSC, ongoing cardiovascular support may be needed due to severe cardiac dysfunction and systemic physiologic derangements from ischemia-reperfusion injury. Venoarterial extracorporeal life support (ECLS) has been successfully used in trauma patients with prehospital or in-hospital HiTCA,[28,29] with a published survival rate of 42% to 63% in a recent systematic review.[30]

We hypothesized that there will be similar rates of ROSC and short-term survival after HiTCA treated with SAAP therapy using either FWB or HBOC-201. Secondarily, we assessed the feasibility of conversion from SAAP to ECLS to provide additional ongoing hemodynamic support. We hypothesized that SAAP followed by conversion to ECLS would be feasible and promote reversal of lactic acidosis over the study period.

METHODS

Study Design and Overview

This study was approved by the Oregon Health and Science University Institutional Animal Care and Use Committee. Twenty-six fasting male Yorkshire swine (*Sus scrofa*, 78.8 [3.9] kg) were obtained from a single source animal vendor (Oakhill Genetics, Ewing, IL). Swine were randomly allocated into two groups (FWB and HBOC-201). Investigators were blinded to randomization during preparatory phases. The study protocol was divided into five phases: preparation, injury, intervention, damage control surgery (DCS) with concurrent FWB resuscitation, and critical care (Fig. 1).

After sedation, induction of anesthesia, preparation, and 10-minute stabilization, a liver injury was performed followed by controlled hemorrhage to induce HiTCA. Animals were then randomized and resuscitated in accordance with their intervention group. The prehospital phase consisted of 20 minutes from SAAP intervention, followed by a 40-minute DCS and DCR phase, then a subsequent 260-minute critical care phase for a total study period of 320 minutes.

Experimental Preparation

Sedation and analgesia were achieved with intramuscular Telazol (8 mg/kg; Zoetis Services, Parsippany, NJ) and intramuscular buprenorphine (0.025 mg/kg). Animals were intubated and general anesthesia was maintained using continuous inhaled isoflurane (1–3%) until HiTCA was achieved. Tidal volumes were set at 6 mL/kg to 8 mL/kg, and end-tidal CO_2 ($EtCO_2$) was maintained in a range of 38 mm Hg to 42 mm Hg until initiation of injury. The inspired fraction of oxygen (FIO_2) was weaned to atmospheric level. After injury initiation, ventilator settings were not altered, allowing $EtCO_2$ to be a surrogate for the effectiveness of resuscitation during the prehospital period.

Following induction, electrocardiographic monitoring was established. The left carotid artery, right femoral artery, right external jugular vein (EJV), left EJV (x2), and right femoral vein were cannulated using ultrasound-guided percutaneous Seldinger technique, with percutaneous catheters placed for blood sampling, physiologic monitoring, and subsequent resuscitation. A pulmonary artery thermodilution catheter (Edwards Lifesciences, Irvine, CA) was inserted through the right EJV sheath. A 14-Fr sheath was inserted into the left femoral artery to facilitate deployment of the SAAP catheter. A right carotid artery cut down was performed to place an ultrasonic flow probe (Transonic Systems Inc, Ithaca, NY). A transesophageal defibrillation probe was fashioned by rolling the posterior external defibrillator pad (Zoll, Chelmsford, MA) around a 20-Fr plastic tube stiffened by a flexible metal stylet. The anterior defibrillation pad was placed on the anterior left chest, and the posterior pad was lubricated using electrically conductive gel and inserted into the esophagus so that the pad was situated posterior to the heart.

Surgical Preparation

In accordance with the established swine model of Non-Compressible Torso Hemorrhage (NCTH), a midline laparotomy and splenectomy were performed, four abdominal wall laparoscopic ports were placed, then the abdomen was closed.[27] Based on surface measurements, the SAAP catheter

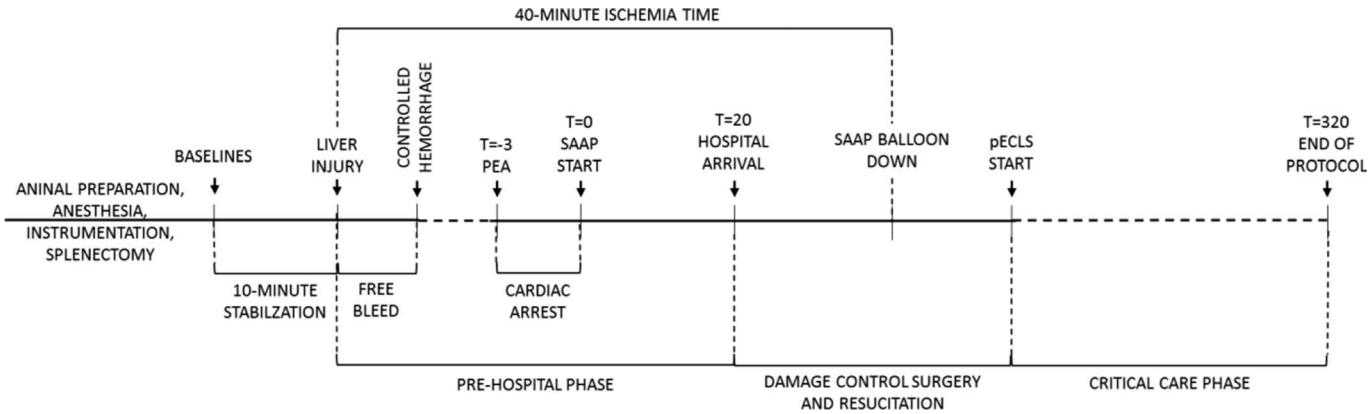

Figure 1. Study protocol timeline. PEA, pulseless electrical activity.

was inserted into the left femoral sheath with the deflated aortic balloon advanced to the thoracic aorta. A 10-minute stabilization period was observed prior to obtaining baseline blood samples and physiologic measurements.

Injury: Creation of NCTH and HiTCA

The abdomen was insufflated to a pressure of 15 mm Hg. The left lateral lobe of the liver was visualized then transected 3 cm to 4 cm away from the hilum using laparoscopic scissors, creating a lethal grade IV liver injury. The abdomen was then rapidly desufflated, all ports were removed, and the incisions were approximated using staples. After 5 minutes, a controlled hemorrhage was initiated at 1 $mL \cdot kg^{-1} \cdot min^{-1}$ to 2 $mL \cdot kg^{-1} \cdot min^{-1}$ until cardiac arrest was achieved. Cardiac arrest was defined as no pulsatile waveforms on the carotid arterial pressure tracing. At that time, isoflurane was stopped.

Intervention

At t = 0, 3 minutes after onset of HiTCA, animals were randomly allocated to one of two groups: (1) SAAP with up to 6 L of oxygenated FWB, or (2) SAAP with up to 6 L of oxygenated HBOC-201. In both groups the intra-aortic balloon catheter (11.5-Fr outer diameter, 7.5-Fr inner diameter, 80 cm long with a 17-mL aortic occlusion balloon (Vention Medical Inc., Denver, CO) was deployed so that the inflation of the balloon occluded Zone 1 of the aorta as defined by Morrison et al.[11] Immediately following balloon inflation, a 50-mL bolus of lactated Ringer's solution was rapidly infused through the SAAP catheter to close the aortic valve, optimizing coronary artery perfusion and reducing left ventricular distension.[14]

a) FWB group: Resuscitation with oxygenated, room-temperature FWB infused in conjunction with a 1% calcium chloride ($CaCl_2$) at a ratio of 8:1 to achieve a total infusion rate of 10 $mL \cdot kg^{-1} \cdot min^{-1}$.[14] $CaCl_2$ was required to chelate citrate in stored FWB and prevent ionized hypocalcemia, which was combined with FWB immediately prior to infusion.
b) HBOC-201 group: HBOC-201 solution was prepared by dilution in lactated Ringer's solution to achieve an Hemoglobin (Hgb) of 8.5 g/dL. Resuscitation with oxygenated, room-temperature HBOC-201 was initiated at a rate of 10 $mL \cdot kg^{-1} \cdot min^{-1}$.[14]

Selective Aortic Arch Perfusion Circuit

Bespoke SAAP circuits were constructed, consisting of a 3-L reservoir (Belmont Instrument Corp., Billerica, MA), a Cardiohelp system and HLS-7 circuit (Maquet Inc., Wayne, NJ), and MASTERFLEX peristaltic pumps (Cole-Parmer, Vernon Hills, IL). This apparatus included recirculation pathways and ports to convert the SAAP resuscitation into arteriovenous ECLS (Supplemental Digital Content 1, Figure 1, http://links.lww.com/TA/B380).

Prehospital Resuscitation Protocol and Endpoints

Selective aortic arch perfusion resuscitation with either oxygenated FWB or HBOC-201 was maintained until ROSC was achieved. Return of spontaneous circulation was defined as Systolic Blood Pressure (SBP) greater than 50 mm Hg with pulsatile carotid waveforms. If ROSC was not achieved by 2 minutes, or ventricular fibrillation developed, intra-aortic epinephrine (0.5 mg) was administered every 30 seconds (up to 2 mg maximum), as needed, until ROSC. If ventricular fibrillation occurred, biphasic defibrillation (200 J) was performed and repeated as necessary to achieve an organized electrocardiographic rhythm. Once ROSC was achieved, continuous inhaled isoflurane was restarted.

If following ROSC, the SBP dropped below 90 mm Hg or the MAP decreased below 50 mm Hg, a 250-mL bolus of oxygenated FWB or HBOC-201 was administered via the SAAP catheter up to 2 L. Boluses of FWB were given in conjunction with 1% $CaCl_2$, as previously described. No other interventions were performed during the prehospital phase.

DCS Phase

After the 20-minute prehospital phase, animals underwent simultaneous exploratory laparotomy and resuscitation with up to 3 L of warmed intravenous FWB with concurrent 1% $CaCl_2$. The FIO_2 was increased to 1.0. Resuscitation was titrated to SBP greater than 90 mm Hg and MAP greater than 60 mm Hg. Low ionized calcium (iCa) < 0.9 g/dL was treated with 1 g 10% intravenous $CaCl_2$. Profound acidosis (pH < 7.10) was treated with 50 mL of 8.4% sodium bicarbonate solution. Hyperkalemia (K^+ > 5.5 mEq/L) was treated with 10 U of regular insulin and 50 mL of 50% dextrose solution. Hypoglycemia (serum glucose, <3 mmol/L) was treated with 50 mL of 50% dextrose solution.

Damage control surgery laparotomy was performed, with rapid evacuation of intra-abdominal shed blood and hemostasis of the liver injury using manual pressure and hemostatic clamps. Hemoperitoneum was collected and weighed. After clamping, the liver was packed with laparotomy sponges. The SAAP catheter balloon was deflated after a minimum of 40 minutes of abdominal organ ischemia. Balloon deflation time was 20 minutes to 30 minutes after SAAP initiation and adjusted within this range based on variable pre-SAAP injury time. This adjustment standardized total time of hypotension and abdominal ischemic burden. Balloon deflation was only initiated after blood pressure resuscitation targets were met. Hypotension was treated with epinephrine injection or norepinephrine infusion for concurrent Systemic Vascular Resistance (SVR) less than 80% of baseline and dobutamine infusion for cardiac output (CO) less than 80% of baseline despite fluid resuscitation.

Conversion to ECLS

A 15-Fr venous ECLS catheter was placed in the right femoral vein and advanced to the inferior vena cava. Animals were heparinized to achieve an activated clotting time of twice the baseline level. Extracorporeal life support was initiated at a flow rate of 500 mL/min, which was the maximum flow rate achievable at 400 mm Hg given the resistance from the SAAP catheter and the intrinsic aortic pressure post-ROSC.

A urinary catheter was inserted via cystotomy to track urine output. A temporary abdominal closure was performed using a sterile clear plastic cover secured over the bowel to minimize insensible fluid losses.[40]

Critical Care Phase

After DCS and DCR, experimental treatment was continued using simulated critical care algorithms. Packed red blood cells (up to 6 units) were administered for Hgb less than 7 g/dL.

Fresh frozen plasma (FFP) (up to 6 units) was given for SBP less than 90 mm Hg with Hgb ≥ 7 g/dL. Norepinephrine, up to 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$, was infused to maintain SBP greater than 90 mm Hg if animals were not fluid responsive and SVR less than 80% of baseline. Dobutamine, up to 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$, was infused for inotropic support if the animal was not fluid responsive and CO less than 80% of baseline. FIO_2 was titrated to maintain a normal PO_2 based on Arterial Blood Gas (ABG)s. Interventions for profound acidemia, hyperkalemia, hypocalcemia, and hypoglycemia were continued as described in the DCS Phase. Active warming was achieved using a heated water-circulating blanket system. End of study was defined as 320 minutes post-SAAP intervention at which point animals were euthanized using sodium pentobarbital per institutional protocol. Following euthanasia, the liver was removed and weighed to quantify the liver transection.

Data Acquisition

A data acquisition system was used to record high-frequency (500 Hz) data for arterial blood pressure, EKG tracing, and carotid blood flow (BIOPAC Goleta, CA). Other variables were recorded at 60-second intervals including heart rate (HR), $ETCO_2$, central venous pressure, CO, SVR, stroke volume, central venous oxygen saturation (SvO_2), and core temperature.

Arterial blood gas (pH, PO_2, K+, iCa, lactate, base deficit) samples were obtained at baseline after a 10-minute stabilization period, 5 minutes after SAAP intervention (t = 5 minutes), at arrival to hospital (t = 20 minutes), and every 30 minutes afterward until the end of the protocol.

Study Outcomes

Primary outcomes were rate of ROSC and end of experiment survival. Secondary outcomes included correction of hemodynamic derangements (HR, SBP, MAP, CO, SVR, carotid flow, SvO_2, amount of vasopressor medications) and metabolic derangements (pH, lactate, base deficit, iCa, K+, glucose) as well as resuscitation volumes (total volume of resuscitation during prehospital, DCS, and critical care phases of the experiment).

Statistical Analysis

Data were analyzed using SigmaPlot 12.0 (Systat Software, Inc, San Jose, CA). An a priori power analysis was performed (Fisher's exact test) to detect a 40% difference in survival. Survival was analyzed with a log-rank test in conjunction with a Kaplan Meier survival plot. Categorical and continuous variables were analyzed using Fisher's exact test and two-tailed Student's *t* tests, respectively. Significance was defined as alpha less than 0.05.

RESULTS

Baseline and Injury Characteristics

Baseline and injury characteristics are presented in Table 1. Physiologic and laboratory baseline values were similar between groups. There were no significant differences in liver injury parameters, or total blood loss per kg of body weight.

Induction of HiTCA

Cardiac arrest and resuscitation characteristics are presented in Table 2. Following injury, time to cardiac arrest was similar. During the 3-minute period of cardiac arrest, cardiac dysrhythmias were common; asystole occurred in 25% of the FWB group versus 21% of the HBOC-201 group ($p = 1.000$) and ventricular fibrillation occurred in 33% of the FWB group and 7% of the HBOC-201 group prior to intervention ($p = 0.148$).

Aortic Hemostasis and Resuscitation Using SAAP

Data collected in the SAAP intervention phase of the experiment are shown in Table 2. Time to initiation of SAAP therapy was similar between groups. Return of spontaneous circulation was achieved in 100% of FWB animals versus 86% of HBOC-201 animals ($p = 0.483$). The rate of ventricular fibrillation either before or immediately after initiation of SAAP was similar between groups (42% in FWB, 50% in HBOC-201). Two animals in the HBOC-201 group went into refractory ventricular fibrillation despite repeated defibrillation attempts and intra-aortic epinephrine. The time required to achieve ROSC was similar between groups. Fresh whole blood animals required significantly more volume during initial SAAP resuscitation to achieve ROSC as compared with HBOC-201 ($p = 0.034$), however, required fewer additional post-ROSC bolus resuscitation during the remainder of the prehospital period ($p = 0.306$) resulting in similar prehospital total fluid volumes administered between groups. We observed a rapid improvement in carotid blood pressure, HR, and carotid flow in both groups after initiating SAAP therapy (Fig. 2). Carotid flow and HR in the FWB group were lower than the HBOC-201 group during the prehospital period. Carotid systolic and diastolic pressures were similar between groups. Prehospital survival was similar in both groups, with 100% survival for FWB and 86% with HBOC-201 ($p = 0.483$). Both prehospital deaths in the HBOC-201 group occurred due to refractory ventricular fibrillation.

DCS and Resuscitation

Damage control surgery was performed in all animals that achieved ROSC. Two animals in the HBOC-201 group with initial successful ROSC were excluded during DCS due to equipment failure (one due to calcium pump failure, one due to ECLS circuit failure). The single death in the FWB group was caused by vena caval thrombosis and pulmonary embolism; the two deaths in the HBOC-201 group occurred during DCS and were both secondary to profound hypotension refractory to fluid resuscitation and vasopressors. Time to definitive hemorrhage control and total volume of FWB resuscitation during DCS was similar between groups. All animals surviving DCS in both groups were successfully transitioned to ECLS after placement of a femoral venous catheter.

Critical Care Phase

Figure 3 depicts a Kaplan-Meier survival curve for both experimental groups. Overall survival was not significantly different between groups, with 92% survival in the FWB group versus 67% in the HBOC-201 group ($p = 0.119$). Two FWB animals surviving to 320 minutes were decompensating with very high lactates. Eight animals in each group were stable or improving at critical care phase end.

Trends of serum lactate and pH over time are demonstrated in Figure 4. Serum lactate was significantly higher than baseline values at the end of the prehospital period in both groups, peaked at 80 minutes, then decreased over the critical

TABLE 1. Baseline, Injury, and End Experiment Characteristics

Parameter	Baseline					
Preparation	**FWB (n = 12)**	**HBOC-201 (n = 14)**	***p* value**	**End of Experiment**		
Weight, kg	77.4 (3.7)	80.0 (3.7)	0.094			
Spleen weight, g	719 (146)	758 (150)	0.509			
Total preparation time, min	134 (31)	138 (32)	0.738			
Physiologic parameters	FWB (n = 12)	HBOC-201 (n = 14)	*p* value	FWB (n = 11)	HBOC-201 (n = 8)	*p* value
HR, bpm	103 (26)	101 (18)	0.827	131 (23)*	145 (26)*	0.243
Systemic SBP, mm Hg	99.8 (8.6)	97.6 (9.5)	0.533	90.4 (15.1)*	88.3 (10.1)*	0.736
Femoral SBP, mm Hg	97.9 (10.8)	97.8 (15.9)	0.981	60.6 (18.8)*	65.1 (22.7)*	0.643
Pulmonary SBP, mm Hg	26.9 (6.6)	29.8 (5.3)	0.232	29.9 (10.6)	40.6 (6.32)*	0.021†
Carotid flow, mL/min	190 (31)	184 (44)	0.685	111 (57)*	178 (68)	0.033†
CVP, mm Hg	11.5 (1.8)	11.9 (2.5)	0.689	10.3 (1.9)	9.6 (2.4)	0.513
CO, L/min	6.13 (1.07)	6.07 (0.84)	0.871	5.66 (1.29)	5.18 (0.88)*	0.391
SVR, dyn·s/cm	854 (173)	858 (184)	0.953	623 (191)*	625 (175)*	0.985
$EtCO_2$, mm Hg	41.0 (2.6)	41.3 (2.6)	0.781	34.5 (7.2)*	39.1 (3.8)	0.119
Temperature, °C	38.2 (0.9)	38.1 (1.4)	0.963	37.2 (3.4)	38.5 (1.6)	0.335
pH	7.46 (0.03)	7.46 (0.03)	0.805	7.31 (0.16)*	7.31 (0.10)*	0.980
Po_2, mm Hg	99.4 (15.5)	103.5 (19.3)	0.559	250.2 (70.3)*	239.1 (66.2)*	0.733
pCO_2, mm Hg	41.1 (2.0)	41.1 (2.1)	0.958	39.8 (6.2)	45.0 (6.7)	0.099
Hgb, g/dL	10.3 (0.9)	10.1 (0.8)	0.534	9.5 (1.3)	9.4 (0.8)	0.935
Potassium, mmol/L	4.0 (0.2)	4.1 (0.3)	0.568	5.1 (0.8)*	5.1 (0.7)*	1.000
iCa, mmol/L	1.32 (0.04)	1.30 (0.04)	0.188	1.28 (0.06)	1.31 (0.08)	0.388
Lactate, mmol/L	2.2 (0.8)	1.9 (0.5)	0.290	10.4 (8.2)*	7.5 (3.5)*	0.367
Base deficit	5.4 (1.8)	5.2 (2.4)	0.845	−4.9 (9.7)*	−3.5 (5.2)*	0.711
Serum glucose, mmol/L	5.0 (1.2)	5.5 (0.9)	0.194	4.8 (2.1)	4.3 (2.1)	0.669
Injury characteristics	FWB (n = 12)	HBOC-201 (n = 14)	*p* value			
Transection duration, s	58.8 (20.5)	58.9 (17.1)	0.997			
Time to HiTCA, sec	862 (350)	816 (166)	0.66			
Resected lobe, %	65.9 (10.8)	70.2 (6.0)	0.24			
Controlled hemorrhage, mL	794 (542)	778 (311)	0.934			
Hemoperitoneum, mL	3450 (737)	2990 (297)	0.08			
Total blood loss, mL/kg	54.9 (14.1)	46.8 (6.4)	0.107			
Cardiac rhythm immediately prior to intervention	FWB (n = 12)	HBOC-201 (n = 14)	*p* value			
Perfusable rhythm, n (%)	4 (33)	6 (43)	0.701			
Ventricular fibrillation, n (%)	4 (33)	1 (7)	0.148			
Agonal, n (%)	1 (8)	4 (29)	0.330			
Asystole, n (%)	3 (25)	3 (21)	1.000			

* Statistically significant difference between end of experiment and baseline parameter within the experimental group. Values are displayed as mean (SD) unless otherwise stated.
† Statistically significant difference between FWB and HBOC-201 groups.
CVP, central venous pressure.

care phase of the experiment. Serum lactate was similar between groups at baseline, 80 minutes (peak), and end of experiment. In both groups, end of experiment lactate was significantly higher than the baseline level (10.1 [8.2] mmol/L vs. 2.2 [0.7] mmol/L, $p = 0.008$ FWB and 7.5 [3.5] mmol/L vs. 1.9 [0.5] mmol/L, $p = 0.002$ HBOC-201]. Compared with 80 minutes (peak), lactate levels significantly improved by end of experiment in the HBOC-201 group ($p = 0.001$) but not in the FWB group ($p = 0.104$), influenced by the two unstable FWB animals.

Serum pH significantly decreased after HiTCA and subsequent SAAP therapy, nadiring at 50 minutes. In both groups, pH significantly increased from 50 minutes to end of experiment. However, end of experiment pH in both groups was significantly lower than baseline (7.31 [0.16] vs. 7.46 [0.03], $p = 0.007$ FWB and 7.31 [0.09] vs. 7.46 [0.03], $p = 0.003$ HBOC-201). There were no significant differences in pH between groups at baseline, 50 minutes, or 320 minutes. Similar amounts of 8.4% sodium bicarbonate were given in each group.

The amounts of FFP, norepinephrine, dobutamine, epinephrine, 50% dextrose, and insulin were similar between groups. Total urine output between groups was also similar between groups.

When comparing end of experiment physiologic and laboratory parameters between groups, there was a significant elevation in pulmonary artery pressure and carotid flow in the HBOC-201 group, compared with FWB (Table 1). In the HBOC-201 group, pulmonary artery pressures were significantly higher than baseline (41 [6] mm Hg vs. 30 [5] mm Hg; $p = 0.021$) and carotid flow was similar to baseline level (178 [68] mL/min vs. 184 [44] mL/min; $p = 0.305$). There were no other significant differences in end of experiment physiologic parameters between groups.

TABLE 2. SAAP Therapy, DCS, DCR, and ICU

Parameters	FWB	HBOC-201	Statistical Test
SAAP intervention	FWB (n = 12)	HBOC-201 (n = 14)	*p* value
Perfusate Po_2, mm Hg	730 (48)	788 (44)	0.004*
Perfusate Hgb, g/dL	8.8 (0.6)	8.7 (0.2)	0.483
Perfusate potassium, mmol/L	6.3 (1.3)	4.3 (0.21)	<0.001*
Perfusate calcium, mmol/L	0.07 (0.02)	1.03 (0.06)	<0.001*
Time from HiTCA to SAAP, s	183 (2.27)	182 (1.05)	0.111
Time to ROSC, s	262 (217)	133 (89.3)	0.069
SAAP volume to ROSC, mL	2,180 (1060)	1,430 (469)	0.034*
SAAP bolus, mL	83 (163)	177 (264)	0.306
Total SAAP volume, mL	2,260 (1140)	1,600 (480)	0.079
ROSC, n (%)	12 (100)	12 (86)	0.483
DCS and resuscitation	FWB (n = 11)	HBOC-201 (n = 8)	*p* value
Time to definitive control, min	8.88 (1.59)	8.98 (2.74)	0.930
Ischemia time, min	43.6 (3.3)	42.5 (1.8)	0.408
Need for relaparotomy, n (%)	1 (9)	2 (25)	0.586
DCS FWB, mL	2,974 (617)	3,271 (505)	0.254
Intensive care phase	FWB (n = 11)	HBOC-201 (n = 8)	*p* value
FFP, mL	1,659 (392)	1,500 (231)	0.321
Norepinephrine, mg	3.9 (3.2)	5.2 (3.7)	0.422
Dobutamine, mg	30.8 (66.4)	57.4 (60.8)	0.384
Epinephrine, mg	0.8 (0.8)	0.6 (0.5)	0.599
50% Glucose, mL	104.5 (68.8)	100.8 (54.3)	0.899
8.4% Sodium bicarbonate, mL	63.7 (80.9)	31.3 (25.9)	0.293
Insulin, units	10.9 (0.7)	8.9 (0.6)	0.503
Urine output, mL	189 (234)	96 (112)	0.297
Complications	FWB (n = 12)	HBOC-201 (n = 12)	*p* value
Bleeding, n (%)	2 (17)	3 (21)	1.000
Thrombosis, n (%)	1 (8)	0 (0)	1.000
Death, n (%)	1 (8)	4 (33)	0.317

* A statistically significant difference between the FWB and HBOC-201 experimental groups. Values are displayed as mean (SD) unless otherwise stated.

When comparing end of experiment parameters to baseline values within groups, there were significant differences in both the FWB and HBOC-201 animals (Table 1). Heart rate was significantly increased in both groups and carotid SBP was significantly lower in both groups. Carotid blood flow was significantly lower in the FWB group but not the HBOC-201 group. Cardiac output was significantly decreased in the HBOC-201 group, but not the FWB group. SVR was significantly lower in both groups. There were no significant differences in temperature, hemoglobin, or iCa in either group.

Complications

There were two bleeding complications in the FWB group, both occurring after heparinization: one animal developed a retroperitoneal hematoma discovered on necropsy and a second had bleeding from the liver edge requiring relaparotomy for hemorrhage control. There were three bleeding complications in the HBOC-201 group, all occurring after heparinization: one had rebleeding from the liver edge requiring relaparotomy for hemorrhage control, and two animals had abdominal wall bleeding requiring relaparotomy. There was one thrombotic event in the FWB group prior to heparinization and conversion to ECLS with formation of fatal pulmonary embolism and thrombosis of the vena cava, which was confirmed on necropsy.

DISCUSSION

Selective aortic arch perfusion is efficacious using either FWB or HBOC-201 in the reversal of HiTCA in the setting of NCTH in this experimental animal model. Selective aortic arch perfusion using both FWB and HBOC-201 achieved excellent rates of ROSC (100% vs. 86%) and short-term survival during a 320-minute study period (92% vs. 67%). However, there were significant physiologic derangements from the ischemia-reperfusion injury that were still detectable after 5 hours.

Treatment for the range of hemorrhagic shock to HiTCA should also be managed by consideration of a continuum of support options for hemostasis and resuscitation (Supplemental Digital Content 2, Figure 2, http://links.lww.com/TA/B381). After the balloon is inflated but without administration of fluids through the distal lumen, SAAP functions similarly to REBOA, which has been shown to be effective in the treatment of severe shock with less morbidity than resuscitative thoracotomy with aortic cross clamping.[31]

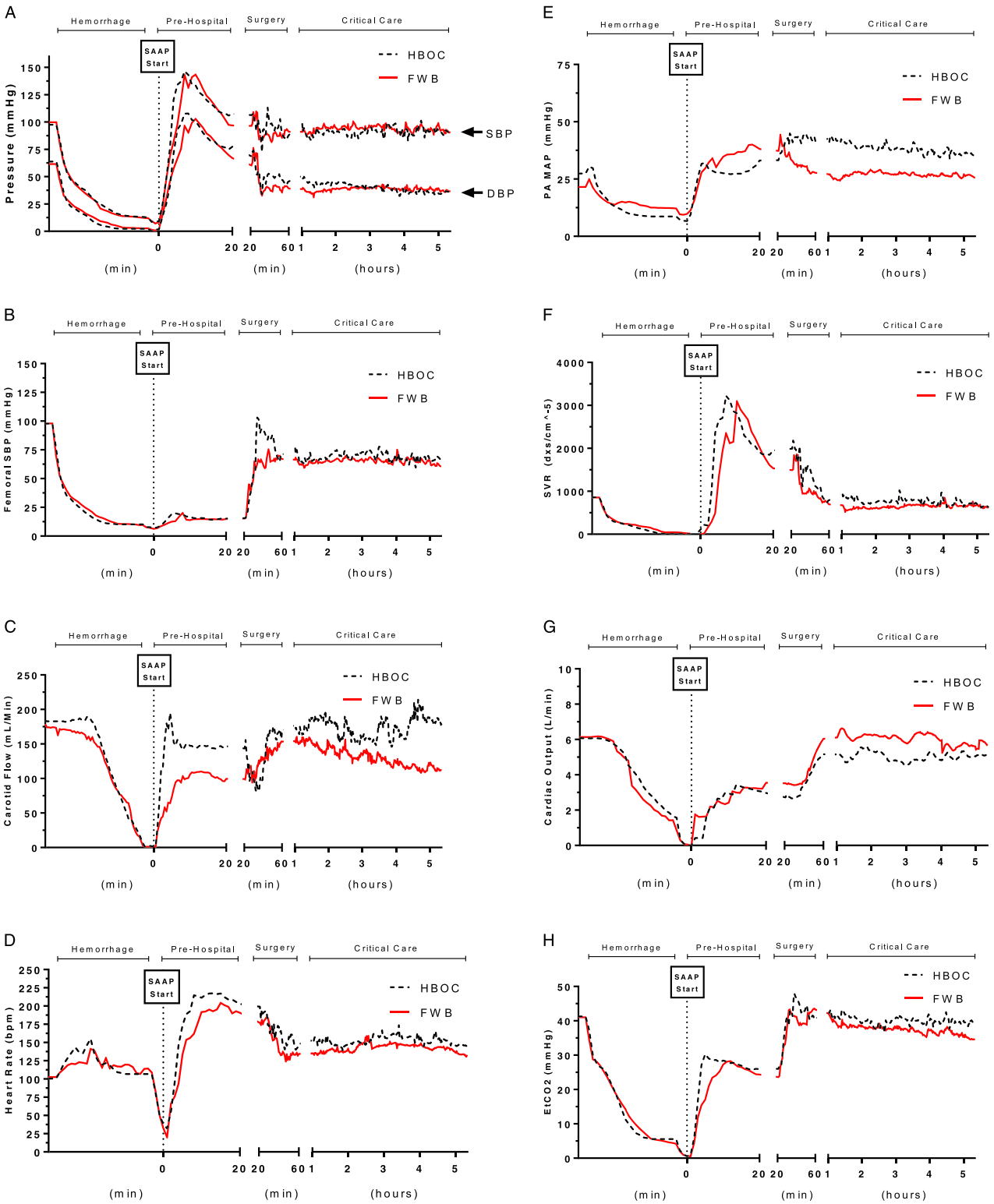

Figure 2. Secondary outcomes. Averaged (*A*) carotid artery systolic and diastolic blood pressure, (*B*) femoral systolic pressure, (*C*) left carotid artery flow, (*D*) HR, (*E*) pulmonary artery mean arterial pressure, (*F*) systemic vascular resistance, (*G*) cardiac output, (*H*) end-tidal carbon dioxide.

In addition to passive aortic occlusion, SAAP provides active intra-aortic resuscitation during cardiac arrest and is highly effective at achieving ROSC and 60 minutes survival after HiTCA in swine models.[17,18] The rates of ROSC and survival after 5 hours using SAAP in this study are significantly higher than published rates of ROSC and survival after HiTCA in both

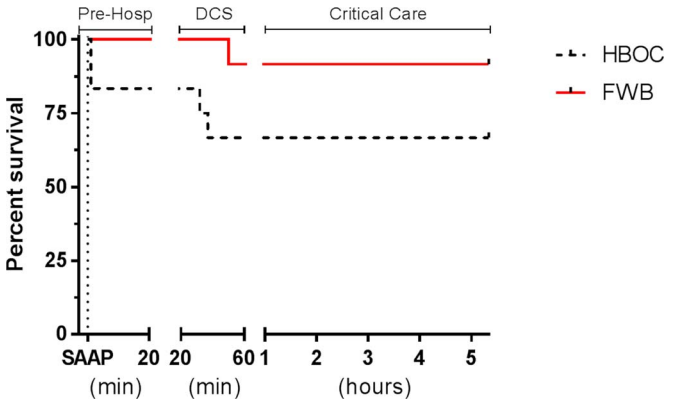

Figure 3. Primary outcome – Overall (320 minutes) survival of HBOC group (n = 14), compared with FWB group (n = 12).

swine and clinical studies using CPR,[6] resuscitative thoracotomy,[5,7] or REBOA in conjunction with a balanced blood product resuscitation.[8,9,17] We also have demonstrated consistent efficacy of achieving ROSC using SAAP in animals with electrocardiographic asystole, which has been previously considered an unsalvageable condition.[32]

Selective aortic arch perfusion is a promising new therapy in achieving ROSC and improving survival after HiTCA, but physiologic derangements caused by ischemia-reperfusion injury cannot be overlooked. The consequences of ischemia-reperfusion injury after balloon occlusion of the aorta are well documented,[33–36] and have led to development of strategies using partial[8,34,42] or intermittent aortic occlusion.[11] However, partial occlusion of the aorta may decrease survival in the prehospital setting due to inadequate hemorrhage control.[33] Further work is needed to determine the optimum balance between hemostasis and ischemic sequelae in HiTCA, as previous studies have used less severe models of hemorrhagic shock.

In this study, we also demonstrated the ability to transition from aortic occlusion and resuscitation to ongoing cardiopulmonary support with partial venoarterial ECLS using the SAAP catheter functioning as the arterial cannula, which provided 500 mL/min of support. A higher level of venoarterial ECLS support may be helpful in the setting of severe physiologic derangements secondary to HiTCA and ischemia-reperfusion injury.[29]

Additionally, the complexity of prehospital administration of intra-aortic oxygenated FWB must be considered as SAAP is transitioned from laboratory to clinical settings. Citrate-anticoagulated blood has very low (nondetectable) iCa, yet normal iCa is important to avoid potential refractory ventricular fibrillation.[22] Thus, calcium must be added to blood immediately before infusion. Although not presently FDA-approved, HBOC-201 is isocalcemic and room temperature stable for 3 years.[37] These properties provide significant advantages for SAAP implementation, particularly prehospital.

In this study, HBOC-201 appears to have similar rates of ROSC and short-term survival as FWB, similar physiologic derangements and logistically is much simpler to administer. The only significant variance in physiologic parameters between groups was pulmonary hypertension, which is a known side effect of HBOC-201, due to vasoconstriction and nitric oxide scavenging.[38] Previous studies have demonstrated that sodium nitrate may help counteract this pulmonary vasoconstriction in the setting of hemorrhagic shock.[38] HBOC-201 is currently only approved for clinical use in South Africa. However, it has been used in the United States for compassionate use in patients with severe anemia who refused blood products due to religious beliefs, showing an improvement in survival compared to conventional therapy.[26] Further work is needed to determine the efficacy of HBOC-201 versus standard therapy in prehospital settings where blood products are not available.

Complications

Ventricular fibrillation was a significant confounding factor in this study. Overall, ventricular fibrillation occurred in 67% of animals, including two episodes refractory to repeated defibrillation. Swine have a lower fibrillation threshold as compared to humans.[39] However, ventricular fibrillation in our model was more common than in previous studies utilizing SAAP therapy in a swine model.[17,18] This could be swine model-related or reflect a reperfusion dysrhythmia event. Further studies are needed to determine the effect of SAAP therapy on ventricular fibrillation in this model of NCTH.

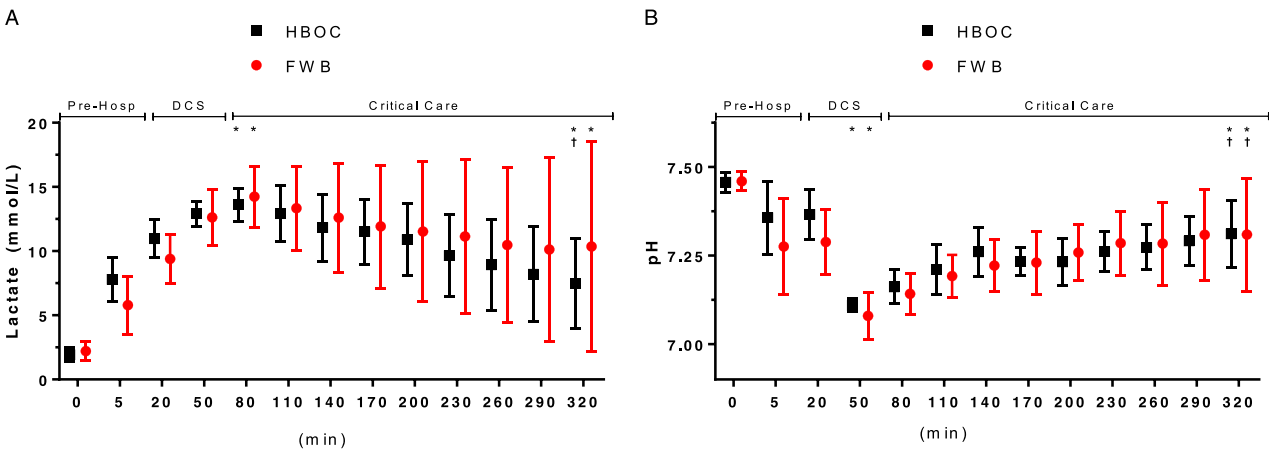

Figure 4. Metabolic changes in response to HiTCA and balloon occlusion of the aorta (*A*) trend in serum lactate over time; (*B*) trend in serum pH over time. * Statistically significant difference from baseline. †Statistically significant difference from peak or nadir.

There were five bleeding complications, all occurring after full anticoagulation with heparin. While rate of bleeding events was similar between groups, further work is needed to determine the effects of HBOC-201 on the coagulation profile in the setting of hemorrhagic shock.

Limitations

Limitations of this study include its translational nature and the use of a swine model of NCTH though the choice of swine as a model was deliberate as swine cardiopulmonary and swine cardiovascular anatomy and physiology are similar to that of humans in response to traumatic injury. Physiologic monitoring used to guide clinical decisions may not be available in clinical settings, especially prior to arrival at a medical treatment facility. However, despite these limitations, this study builds on the existing evidence for the effectiveness of SAAP in HiTCA and future human trials.

CONCLUSION

Selective aortic arch perfusion utilizing either FWB or HBOC-201 is a promising therapy for reversal of HiTCA, with potentially significant survival advantages over existing therapies. This animal study demonstrates HiTCA reversed by SAAP, but not without significant physiologic derangements associated with the subsequent ischemia-reperfusion. Further work is needed to determine the therapeutic window for aortic balloon occlusion in the setting of HiTCA, assess neurologic consequences, and streamline the steps needed to initiate SAAP therapy to improve safety and potential efficacy as human clinical trials are pursued.

AUTHORSHIP

J.R., J.M., H.H., T.G. participated in the study design. H.H., J.M., T.G., B.M., S.M., J.R. participated in the data collection. H.H., T.G., J.M., J.R. participated in the data analysis and interpretation. H.H. participated in the drafting of the article. H.H., J.M., T.G., B.M., S.M., J.R. participated in the critical revisions.

ACKNOWLEDGMENTS

We would like to acknowledge Lauren Wilson and Brianne Madtson for their superb technical contribution to the experiments presented here.

FUNDING

This body of work was funded by the Defense Medical Research and Development Program. Award number: W81XWH-16-2-0012.

DISCLOSURE

J.E.M. declares intellectual property interests in SAAP technology. He is also the co-founder of Resusitech, Inc., a medical device company developing SAAP technologies. J.E.M. has also delivered approximately 30 invited lectures on SAAP for resuscitation in medical and traumatic cardiac arrest. For several lectures, travel costs were reimbursed by the inviting organization or the University of North Carolina.

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DISCUSSION

SAMUEL TISHERMAN, M.D. (Baltimore, Maryland): Drs. Agarwal and deMoya, ladies and gentlemen, I'd like to congratulate Dr. Hoops on completing a complex project and an excellent presentation.

We all recognize that patients who exsanguinate to the point of cardiac arrest have a dismal prognosis despite aggressive attempts at resuscitation with airway management, massive transfusions, and resuscitative thoracotomy. Little has changed in our approach to these patients over the last several decades. So what options do we have to save these patients who are currently dying in front of us?

One option is to take the resuscitative thoracotomy to the field, as Drs. Davies and Lockey have done in highly-selected patients in London. Although we generally believe that open chest cardiopulmonary resuscitation (CPR) is superior to closed-chest CPR in trauma patients, this may not be true for patients without obvious thoracic trauma. Is closed chest compressions with Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) a better option? Maybe.

Novel intra-aortic approaches to resuscitation, however, could be game changers. Standard extracorporeal life support (ECLS) could provide circulation but be limited by ongoing hemorrhage. Alternatively, extracorporeal technology could be utilized to perfuse the patient with cold fluid to achieve deep hypothermia to increase tolerance for ischemia, as in Emergency Preservation and Resuscitation for which we have an ongoing trial at Shock Trauma.

This brief discussion of intra-aortic approaches now brings us to another novel approach, Selective Aortic Arch Perfusion (SAAP), presented by Dr. Hoops. In the current study, she and her colleagues utilized a complex, clinically-relevant, large animal model of lethal liver injury, exsanguinating hemorrhage to the point of arrest, resuscitation using SAAP with oxygenated whole blood or Hemoglobin-Based Oxygen Carrier-201 (HBOC-201), followed by damage control laparotomy and conversion to ECLS. They suggest that SAAP with either whole blood or HBOC-201 shows promise and the conversion to at least low-flow ECLS is feasible.

I have several questions for Dr. Hoops.

Number 1. Calcium chloride infusion was used routinely, though it's not needed for humans or even swine in other studies receiving massive transfusion. Is this a unique issue with swine or with SAAP or with both?

Number 2. You discussed the importance of ischemia reperfusion injury in this model, looking at lactate levels, in particular. How can you differentiate between global ischemia from shock and cardiac arrest versus the ischemia from aortic occlusion?

Number 3. Proving equivalence of two therapies is difficult as large numbers of subjects are needed, making this even

more difficult with expensive, complex animal models. I am concerned that there is a trend for worse survival in your HBOC group and changing the outcome of one animal could have led to a statistically significant difference favoring whole blood. In addition, the HBOC group required less volume to achieve restoration of spontaneous circulation and, in your manuscript, had higher pulmonary artery pressures, consistent with the known vasoconstrictive effects of HBOCs. Given the questionable outcome equivalence, potential deleterious vasoconstriction, and lack of approval in the U.S., what are your thoughts about the future of HBOC-201?

Number 4. It's not clear to me why the study included the addition of conversion to ECLS. You already know that the SAAP catheter with a maximum flow of about 500 mls per minute does not provide much hemodynamic support, which the animals in this study didn't even seem to need. How do you see this interface between SAAP and ECLS moving forward? And what about SAAP and Emergency Preservation and Resuscitation?

Number 5. Finally, what is next for SAAP? Are you continuing this work in the lab? As it seems that all the technical aspects of SAAP are feasible with current technology, what is needed before starting a clinical trial?

I would again like to congratulate Dr. Hoops and her colleagues for pushing the field of resuscitation for exsanguinating trauma patients forward. We need this type of creative research. I look forward to more great work from this group.

I'd like to thank the Association for the privilege of the podium.

JEREMY W. CANNON, M.D. (Philadelphia, Pennsylvania): Very nicely presented. Just from a practical standpoint, you describe a reservoir where you have your whole blood or your HBOC. When it gets low how do you keep it from entraining air? Do you have any sort of safety mechanisms? It just seems like if you're in an uncontrolled prehospital environment that could be a real issue. Thank you.

HEATHER E. HOOPS, M.D. (Portland, Oregon): I'd like to thank Dr. Tisherman for the excellent points in the discussion as well as the questions.For the intra-aortic calcium, the perfusate ionized calcium level of the perfuse used in SAAP therapy is 0.07. In contrast to administrating blood intravenously there is no time to equilibrate that calcium when you are perfusing it so close to the coronary arteries.

We found with previous studies with SAAP and swine animals that we needed the intra-aortic calcium to prevent ventricular fibrillation.

SAAP therapy has not been attempted in humans so I cannot comment on the necessity or whether the rates of calcium chloride administration would be the same.

As far as the dysfunction due to the traumatic cardiac arrest versus the ischemia rate perfusion injury of a balloon occlusion, I think this is difficult to determine.

A longer balloon occlusion time in our model development led to irreversible physiologic derangements so I think we still need to do further work to determine a therapeutic window associated with how long we can leave the intra-aortic balloon inflated in the setting of traumatic cardiac arrest.

As far as HBOC, I think our thought for the future of HBOC is to be able to be utilized in settings where fresh whole blood is not available so in austere medical environments where you need something that's room temperature or in Jehovah's Witness patients. It's been using more and more commonly in the U.S. in patients who are refusing fresh whole blood as an alternative to simply crystalloid.

So we envision HBOC being used you know downrange in military settings or internationally or in patients who refuse fresh whole blood moving forward.

In the hospital setting we envision SAAP being used with fresh whole blood as that is the standard of care.

As far as conversion to ECLS, in this study we chose to convert to ECLS using the SAAP catheter. By switching out that catheter to an arterial ECLS cannula, we could provide much more support.

We did this for simplicity reasons but certainly something that could provide more support moving forward in animals or in patients with more physiologic derangements.

For future directions of this study, I think we need to determine the therapeutic window with a balloon occlusion of the aorta. Partial REBOA or partial occlusion versus intermittent occlusion maybe options to increase the therapeutic window associated with balloon occlusion.

I think further work is needed to determine the physiologic consequences of using HBOC versus fresh whole blood on the coagulation pathway as well as markers of tissue ischemia and also to evaluate neurologic outcomes as we try to move towards clinical trials, which there are ongoing efforts to get started.

As far as the niche or the SAAP therapy in the use for the treatment of traumatic cardiac arrest, cardiac arrest due to hemorrhage is a continuum where you have a low-flow state that eventually becomes a no-flow state.

And so adjuncts such as cross-clamping the aorta after resuscitative thoracotomy or endovascular balloon occlusion in the aorta do provide hemorrhage control but we envision SAAP being used when that low-flow state becomes a no-flow state. In other words, a way to achieve ROSC with oxygen delivery to the heart in addition to having hemorrhage control.

And we recognize one of the reasons why we included the ECLS in the study, we recognized that we need to convert that into more ongoing support that does not include ischemia of tissues below the aortic balloon.

Regarding the question regarding safety mechanism for entrapment of air, I think this highlights the complexity of this study as far as calcium co-administration as well as the Belmont blood transfuser (Belmont Medical Technologies, Billerica, MA). In this study, we had one person loading the Belmont with blood or HBOC-201 and we would stop before getting to that six liters.

And so I think as we are moving towards clinical trials more safety mechanisms need to be in place as far as determination of delivery of intra-aortic calcium as well as other safety mechanisms when refining this circuit to be used in clinical trials.

Thank you.

Selective Aortic Arch Perfusion (SAAP)

Endovascular extracorporeal cardiac arrest perfusion for resuscitation of hemorrhage-induced traumatic cardiac arrest and sudden cardiac death/medical cardiac arrest

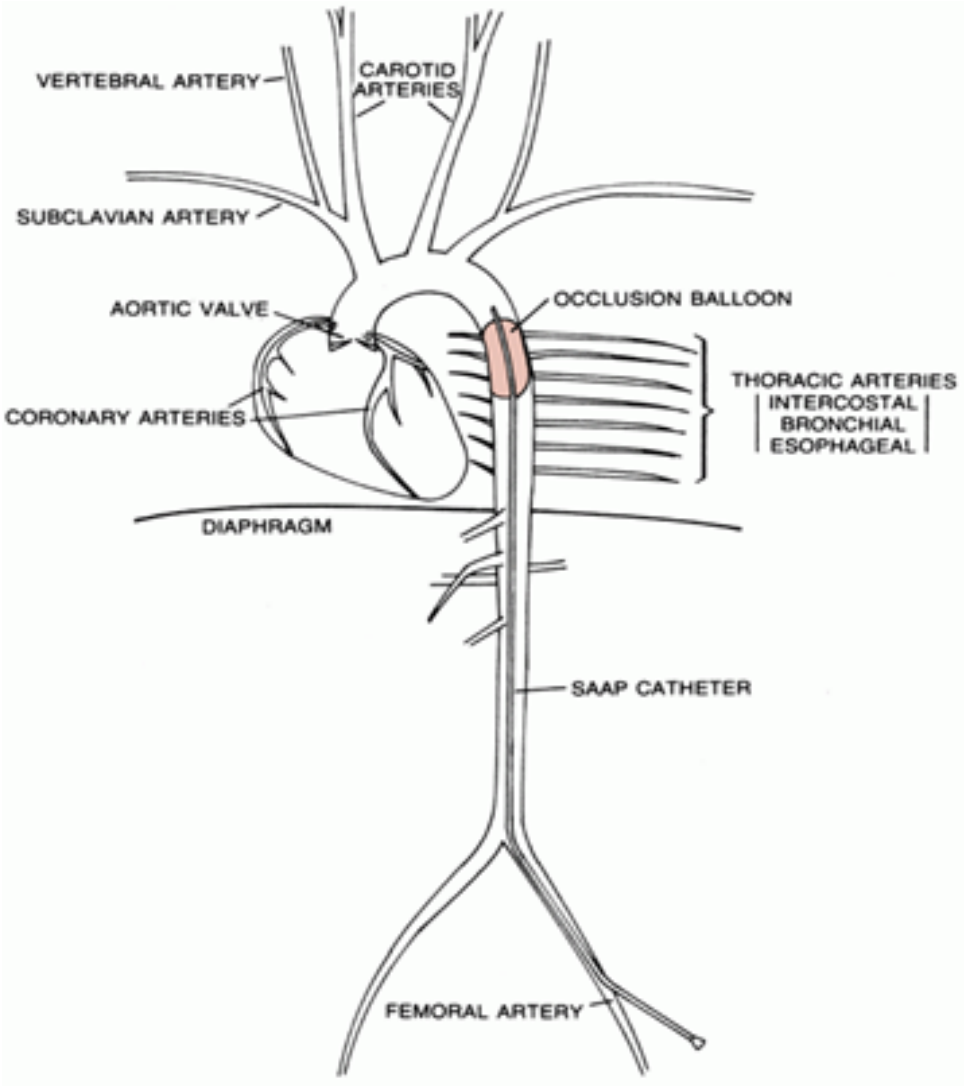
Training Course

Table of Contents

Introduction

Selective Aortic Arch Perfusion (SAAP) is an emerging endovascular resuscitation technique that provides temporary extracorporeal perfusion to the heart and brain during cardiac arrest. The aim of SAAP therapy in the treatment of cardiac arrest is to restore intrinsic cardiac contractility and physiologic range cardiac output, referred to in the resuscitation literature as return of spontaneous circulation (ROSC), with good neurological recovery. SAAP was developed specifically as a cardiac arrest therapy and is applicable to both medical cardiac arrest (e.g., dysrhythmia-induced sudden cardiac death) and hemorrhage-induced (including traumatic) cardiac arrest. A series of SAAP interventions (SAAP modalities) provides a stepwise escalation of extracorporeal perfusion, limited to the aortic arch vessels by the inflated thoracic aortic balloon, that generates higher blood flow to the heart and brain than is achieved by closed-chest cardiopulmonary resuscitation (CPR). The myocardial perfusion during SAAP is greater than the heart receives during normal intrinsic contractility due to the ability to perfuse the heart continuously as opposed to predominantly during the cardiac diastolic phase when the heart is beating normally. This sequence of SAAP modalities is used, as needed, to achieve ROSC, or to provide bridging heart and brain perfusion support until cannulation for prolonged veno-arterial extracorporeal life support (VA-ECLS) if required. The sequential SAAP modalities allow for the extracorporeal perfusion support to be tailored to the needs of the individual cardiac arrest patient such that the level of intervention meets, but does not exceed, the aggressiveness needed for ROSC.

Selective Aortic Arch Perfusion (SAAP)



Selective Aortic Arch Perfusion (SAAP) is an endovascular extracorporeal perfusion technique specifically designed for cardiac arrest resuscitation. SAAP is applicable to both medical and traumatic cardiac arrest.

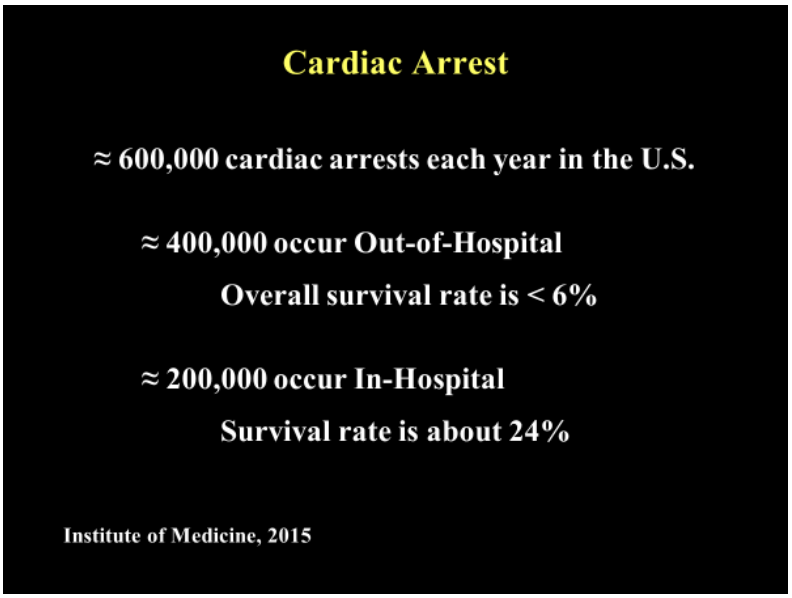
Cardiac Arrest Survival

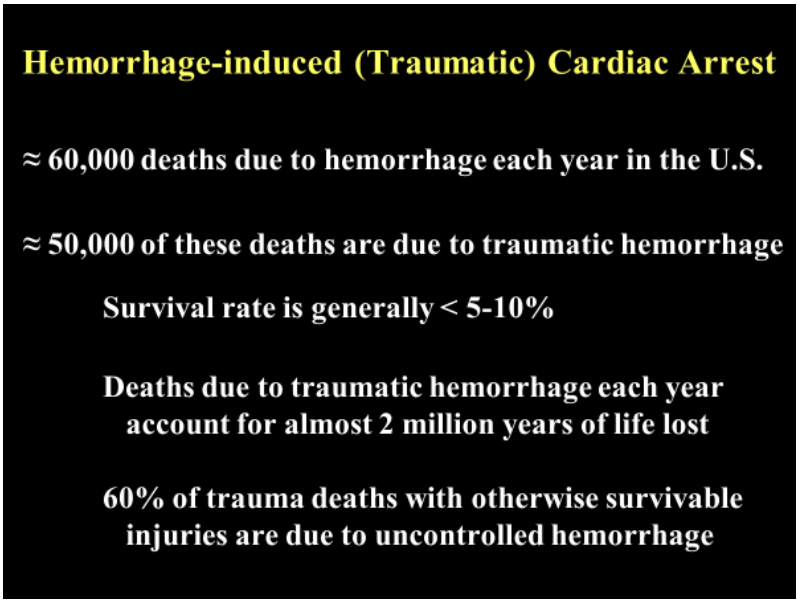
Cardiac arrest is a major public health problem in the United States and throughout the world. According to a 2015 Institute of Medicine Report, there are an estimated 600,000 cardiac arrests each year in the U.S. alone. This includes cardiac arrest due to primary cardiac causes as well as trauma, poisonings and other etiologies. Of these, approximately 400,000 occur outside of a hospital setting and the survival rate overall for this population is less than 6%. There are an estimated 200,000 in-hospital cardiac arrests each year with a survival rate of about 24%.[1] The major limiting factors in achieving a ROSC in medical cardiac arrest are the inadequate myocardial blood flow produced by closed-chest CPR, delays in initiation of bystander CPR, and lack of early defibrillation.

The incidence of cardiac arrest secondary to trauma is estimated to be 60,000 cases/year in the U.S. Reported survival in traumatic cardiac arrest (TCA) is improving but may be even lower than medical cardiac arrest - many of the potentially survivable deaths are due to exsanguination. The major limiting factors in achieving ROSC in hemorrhage-induced TCA (HiTCA) are the diminished effectiveness of closed-chest CPR in the setting of hypovolemia, the deleterious effects of CPR chest compressions in the presence of chest trauma, the lack of hemorrhage control, and the lack of high-volume fluid resuscitation required to revive the non-beating, or inadequately beating, heart.

Severe uncontrolled hemorrhage rapidly leads to a state of profound hypovolemia and shock that if left untreated can result in cardiovascular collapse and death within minutes. Trauma is the leading cause of severe uncontrolled hemorrhage and is responsible for much of the morbidity and mortality in both military and civilian trauma populations. Uncontrolled hemorrhage due to non-

compressible torso hemorrhage (NCTH) is the leading cause of reported preventable death in military combatants and civilian trauma patients with otherwise survivable injuries (predominantly the lack of devastating traumatic brain injury). Survival from HiTCA is currently extremely low, generally estimated to be in the 1-5% range.

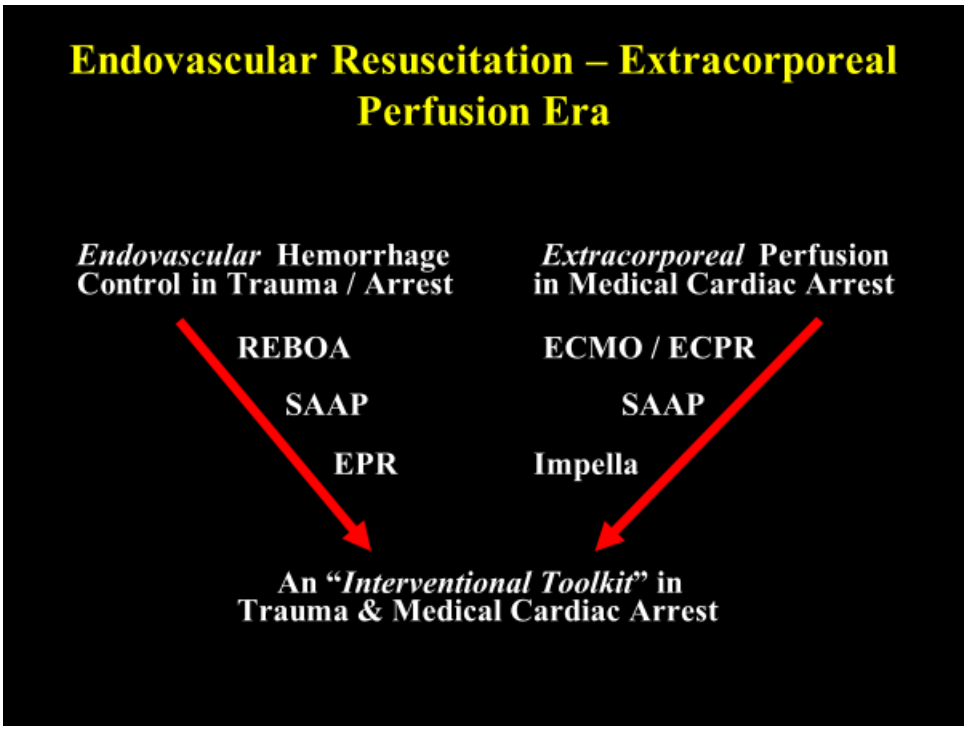


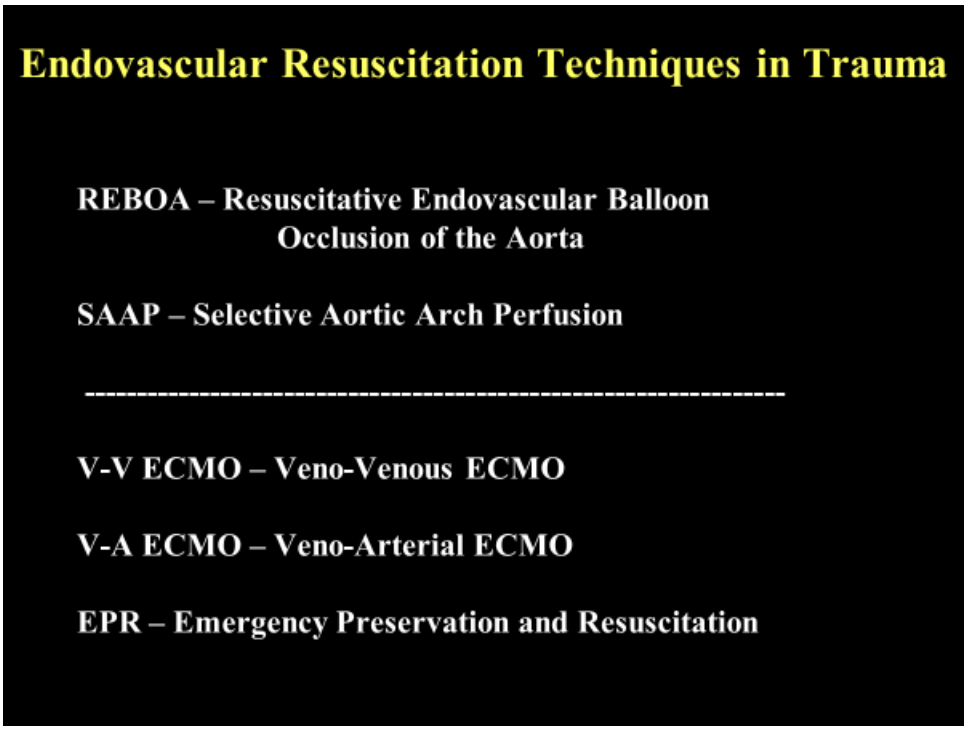


Endovascular and Extracorporeal Resuscitation

The conventional or standard cardiac arrest resuscitation therapies that have been employed in recent decades have several limitations: inadequate CPR blood flow, ineffective drug delivery, and inadequate parameters to guide therapy. All these limitations are addressed to varying degrees by emerging endovascular resuscitation interventions that allow for continuous or intermittent invasive pressure monitoring, extracorporeal perfusion support, and effective drug delivery during cardiac arrest. Endovascular interventions reported in the literature for cardiac arrest resuscitation include: (1) aortic catheterization for hemodynamic monitoring and intra-aortic drug delivery, (2) resuscitative endovascular balloon occlusion of the aorta (REBOA), (3) selective aortic arch perfusion (SAAP), (4) extracorporeal perfusion support: Extracorporeal Membrane Oxygenation (ECMO) and Extracorporeal Life Support (ECLS) are interchangeable terms, and when used in cardiac arrest, is often referred to as extracorporeal-CPR (ECPR), (5) Impella, an intravascular rotor-flow device, and (5) emergency preservation and resuscitation (EPR), induction of profound hypothermia to allow for surgical hemostasis.

This course is focused primarily on SAAP, but the interface with other endovascular resuscitation interventions, particularly REBOA and ECLS/ECMO will be discussed in this course. EPR is a technique that will be touched upon only briefly, and Impella is presently a hospital-based intervention requiring imaging technology for insertion, so this technique will not be discussed in this course. ECLS/ECMO can be either veno-venous or veno-arterial. In this course focused on cardiac arrest, only the use of veno-arterial (V-A) support will be addressed.


Endovascular Resuscitation – Extracorporeal Perfusion Era
Endovascular Hemorrhage Control in Trauma / Arrest
Extracorporeal Perfusion in Medical Cardiac Arrest
REBOA
SAAP
EPR
ECMO / ECPR
SAAP
Impella
An "*Interventional Toolkit*" in Trauma & Medical Cardiac Arrest


Endovascular Resuscitation Techniques in Trauma
REBOA – Resuscitative Endovascular Balloon Occlusion of the Aorta
SAAP – Selective Aortic Arch Perfusion
V-V ECMO – Veno-Venous ECMO
V-A ECMO – Veno-Arterial ECMO
EPR – Emergency Preservation and Resuscitation

END

Cardiac Arrest and Resuscitation Physiology

Cardiac Arrest: Causes and Spectrum

Cardiac arrest ("heart stop") means, strictly speaking, that the heart has ceased to contract and is no longer pumping blood to the organs and tissues of the body, including itself. Cardiac arrest can occur very abruptly, as in sudden cardiac death, or may result from an acute physiologic insult with progressive decompensation resulting in cardiac arrest. In the latter, the time frame of physiologic deterioration can vary from a few minutes to an hour or more, depending upon the cause and severity of the acute event. Lethal ventricular dysrhythmias are generally the cause of sudden cardiac death. However, the list of acute events that cause rapid decompensation to cardiac arrest, albeit over varying time intervals, is considerably longer, including: airway obstruction, pulmonary embolism, toxic exposure, trauma with severe uncontrolled hemorrhage, tension pneumothorax, severe nontraumatic hemorrhage, and central nervous system catastrophes (severe trauma brain injury, high cervical spinal cord injury, massive stroke or intracranial hemorrhage with herniation, vertebro-basilar thrombosis, and impact brain apnea).

The physiologic state and response to resuscitation interventions in any cardiac arrest victim will be influenced by: (1) the nature of the acute insult, (2) the time interval from insult onset to development of cardiac arrest, (3) the time interval from onset of cardiac arrest until initiation of resuscitation interventions, and (4) the baseline physiologic health profile of the victim prior to the acute event.

Cardiac Arrest: Causes & Spectrum

Cardiac Arrest ("heart stop")

- Abrupt onset – Sudden Cardiac Death
  (e.g., ventricular fibrillation)
- Acute rapid decompensation – 2º an acute insult
  (e.g., airway obstruction, overdose, toxin, pulmonary embolism, trauma, CNS)

Cardiac Arrest: Causes & Spectrum

Response to Resuscitation influenced by:

- Nature of insult
- Time interval – Insult to Cardiac Arrest
- Time interval – Cardiac Arrest to Resuscitation
- Baseline physiological health

Healthy individuals normally have substantial physiological reserve and can hemodynamically compensate to some degree early after an acute insult. However, patients with chronic illness and the elderly can have very limited physiological reserve leading to decompensation and cardiac arrest more rapidly.

Cardiac arrest can occur abruptly (commonly called Sudden Cardiac Death) or as the result of an acute event (medical or trauma) with rapid decompensation.

Case Example #1:

An otherwise healthy person who experiences sudden cardiac death due to a dysrhythmia may have essentially no physiological derangements, in terms of cellular metabolism or organ dysfunction, at the onset of cardiac arrest. If the cardiac arrest is witnessed, bystander CPR is initiated, and early electrical countershock is applied with a readily available automated external defibrillator (AED), the patient will very likely have a return of spontaneous circulation (ROSC) and may regain consciousness almost immediately.

The favorable outcome in the case above would be a result of prompt reversal of cardiac arrest (that is, ROSC) from a cardiac arrest state characterized by minimal

ischemic debt (no pre-arrest metabolic debt, immediate CPR to provide temporary blood flow, & short duration of cardiac due to rapid, effective defibrillation).

Case Example #2:

An elderly man with known chronic congestive heart failure and longstanding diabetes is involved in a motor vehicle collision. He has blunt chest and abdominal trauma with pulmonary contusions, a ruptured spleen with large hemoperitoneum, as well as pelvic and femur fractures. Extrication from his vehicle takes 20 min to accomplish. He has progressive hypotension in the field during the extrication that is poorly responsive to field resuscitation, and there is a 20-min transport time to the trauma center. Within 8 min of hospital arrival, he loses pulses and goes into asystolic cardiac arrest on EKG monitor. CPR is initiated.

The prospects for a favorable outcome are considerably less in Case Example #2 due to the combination of pre-insult physiological dysfunction (limited compensatory reserve), severe injuries with refractory hypotension (blood loss and global hypoperfusion), and several minutes of cardiac arrest without rapid reversal. During the time between the insult event and the onset of cardiac arrest, this patient progressively develops a significant metabolic debt due to organ and tissue hypoperfusion. The cardiac arrest time adds further metabolic debt and hemorrhage-induced hypovolemia limits the effectiveness of CPR. Without robust resuscitation interventions, this patient is very unlikely to survive.

True Cardiac Arrest versus Impending Cardiac Arrest

Although the term “cardiac arrest” may seem sufficiently intuitive to those trained in biological and medical sciences, it is worth discussing here, for the purposes of this course. It is not uncommon for clinical states exhibiting profound arterial hypotension, characterized by lack of discernible pulses, to be identified as cardiac arrest states. Strictly speaking, these clinical states of profound arterial hypotension are more accurately defined as states of cardiovascular collapse with “impending” cardiac arrest. This distinction can have significant influence on the response to therapeutic interventions and clinical outcome.

When sudden cardiac death occurs due to the sudden onset of a ventricular dysrhythmia, such as ventricular fibrillation, the forward flow of blood rapidly diminishes over the ensuing seconds as the vasomotor elastic recoil of the aorta and arterial branches cause the arteries to contract down to a static state of minimal or no vasomotor tension. The arterial blood pressure drops rapidly during this vasomotor recoil and plateaus at or just above 0 mm Hg. With the arterial system no longer contracting, the arterial and venous blood pressures essentially equilibrate (possibly differing minimally due to residual resistance across the microvasculature). With no arterial-to-venous pressure gradient present, simple physics dictates that no blood flow can exist. This state, characterized by no myocardial contractions and no forward blood flow, is defined in this course as “true” cardiac arrest for the purposes of this resuscitation course. Although the different insults previously noted that can lead to cardiac arrest may have varying time periods from insult onset to arrest, the cessation of cardiac contractions and the lack of arterial-to-venous pressure gradient to create blood flow are the final commonly shared characteristic features of “true” cardiac arrest.

True Cardiac Arrest vs. Impending Cardiac Arrest

Clinically, cardiac arrest = loss of palpable pulses

"True" cardiac arrest means the heart has stopped contracting

"Impending" cardiac arrest means the heart is still contracting, but no discernible blood pressure

"True vs. Impending" cardiac arrest is a difference that can be significant for endovascular resuscitation

True Cardiac Arrest vs. Impending Cardiac Arrest

Impending cardiac arrest (or profound hypotension) may respond more effectively to resuscitation, including endovascular interventions, than true cardiac arrest.

True vs. Impending cardiac arrest may influence the choice of endovascular resuscitation intervention.

Case Example #3:

A patient with acute severe, uncontrolled hemorrhage could have active cardiac contractions producing a mean arterial pressure of 25 mm Hg with a pulse pressure of only about 10 mm Hg. This patient would most likely have no discernible palpable pulses and no discernible arterial blood pressure using typical noninvasive measurement devices. Nonetheless, this patient does have a beating heart that is generating some, albeit insufficient, blood flow. Yet, even this marked hypoperfusion may sustain cellular survival in preferentially perfused vital organs for a brief time, on the order of minutes, and allow a window for resuscitation efforts. However, without prompt therapy to reverse this state of cardiovascular collapse with impending cardiac arrest, this patient will most likely proceed in a relatively short period of time to a state of true cardiac arrest. With the heart no longer contracting, even the limited blood flow of a profound hypoperfusion state is lost, shortening the time window within which resuscitation efforts must be initiated to offer any prospect of survival.

Patients with a beating heart, despite no discernible blood pressure, are more likely to respond to aggressive resuscitation interventions, and to do so more rapidly. The prospects for recovering hemodynamic stability and surviving improved prospects for survival. In the case example above, the prompt initiation of hemorrhage control and blood transfusions could rapidly result in increased blood pressure and organ perfusion, thus avoiding deterioration to true cardiac arrest. However, if the heart has stopped beating in this same patient, this indicates

a more severe state of organ ischemia, both for the heart and other organs. If true cardiac arrest is present, additional interventions aimed at myocardial perfusion support are required to reverse the cardiac metabolic derangements so that the heart can resume intrinsic contractility. The survival prospects for true cardiac arrest are lower than for the impending cardiac arrest state described above.

The prospects for survival are lower for true cardiac arrest than for impending cardiac arrest.

Cardiac Arrest: Cellular Derangements

The global cessation of blood flow that attends cardiac arrest produces a cascade of derangements in cellular metabolism, electrolyte balance, membrane integrity and nuclear expression. Loss of oxygen delivery leads to rapid depletion of intracellular oxygen required for mitochondrial oxidative phosphorylation and ATP production. The depletion of ATP deprives a vast array of cellular processes of the energy required to sustain cellular homeostasis, including cellular membrane maintenance, ion pump regulation of intracellular electrolyte concentrations, and all cellular anabolic and catabolic processes. Removal of cellular waste products is also suspended leading to accumulation of carbon dioxide and other metabolic waste, like urea. Nuclear triggers for programmed cell death, apoptosis, are activated. Loss of membrane integrity and cellular swelling eventually lead to cellular membrane disruption and cell death.

Figure Reference: Shock Induced Endotheliopathy

Cardiac Arrest: Cellular Derangements

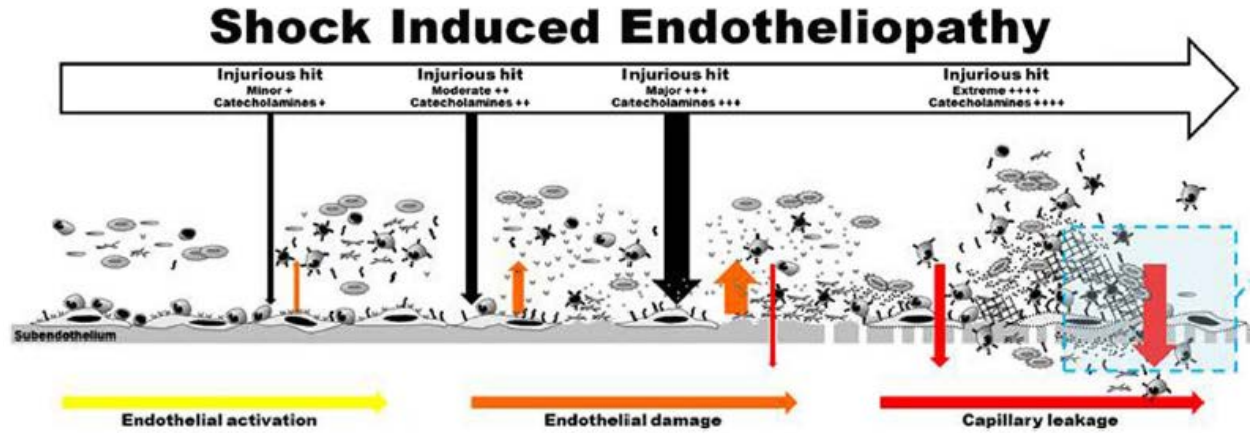
Cellular metabolism
- mitochondrial oxidation → metabolic acidosis

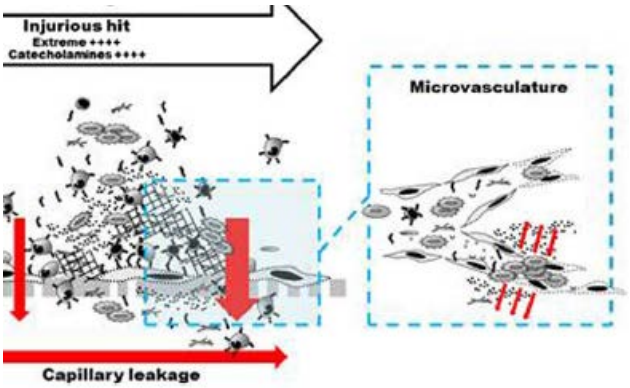
Electrolyte balance
- ion pump regulation

Membrane integrity
- plasma membrane
- mitochondrial → cellular swelling

Nuclear expression → apoptotic pathways

Cellular waste accumulation → carbon dioxide





Cardiac Arrest: Vascular Changes and Organ Dysfunction

As previously described, cessation of cardiac contractility results in immediate changes in the vasculature. Arterial vasomotor recoil causes contraction in the aorta and arterial system until arterial wall tension reaches a minimum plateau. The peripheral arterial system and microvasculature undergo a progressive loss of vasomotor tone over the next several minutes as tissue hypoxia progressively worsens. This peripheral arterial microvascular tone is an important physiologic factor in cardiac arrest and resuscitation because the ability to generate artificial blood flow with closed-chest CPR is significantly dependent upon the degree of residual peripheral arterial vascular tone, as will be discussed below. Capillary leaking and vascular volume shifts ensue as tissue hypoxia persist.

Global organ dysfunction begins with the onset of cardiac arrest and progresses with varying rapidity for different organs depending upon the sensitivity of the specific organ to ischemia, the brain being considered the most sensitive. Inflammatory and immunological responses are triggered. The blood that is lying stagnant within the vasculature exhibits increased viscosity and sludging. Activation of coagulation during such stasis can begin within minutes. The severity of organ dysfunction at the onset of cardiac arrest depends significantly on the etiological factors and time course leading to the cardiac arrest, as well as pre-insult baseline function, consistent with the points described previously.

Cardiac Arrest: Vascular Response

Cardiac Arrest – Loss of forward blood flow

Arterial vascular recoil & rapid fall in arterial pressure

Arterial contraction until minimal or no vasomotor tone

Arterial – Venous pressure equilibration (or near-)

Stasis of blood in the vasculature

Cardiac Arrest: Vascular Response

Tissue hypoxia & acidosis ensue

Microvasculature dilates (arteriolar) & arterial pressure decreases a little more

Endothelial permeability changes

Glycocalyx degradation

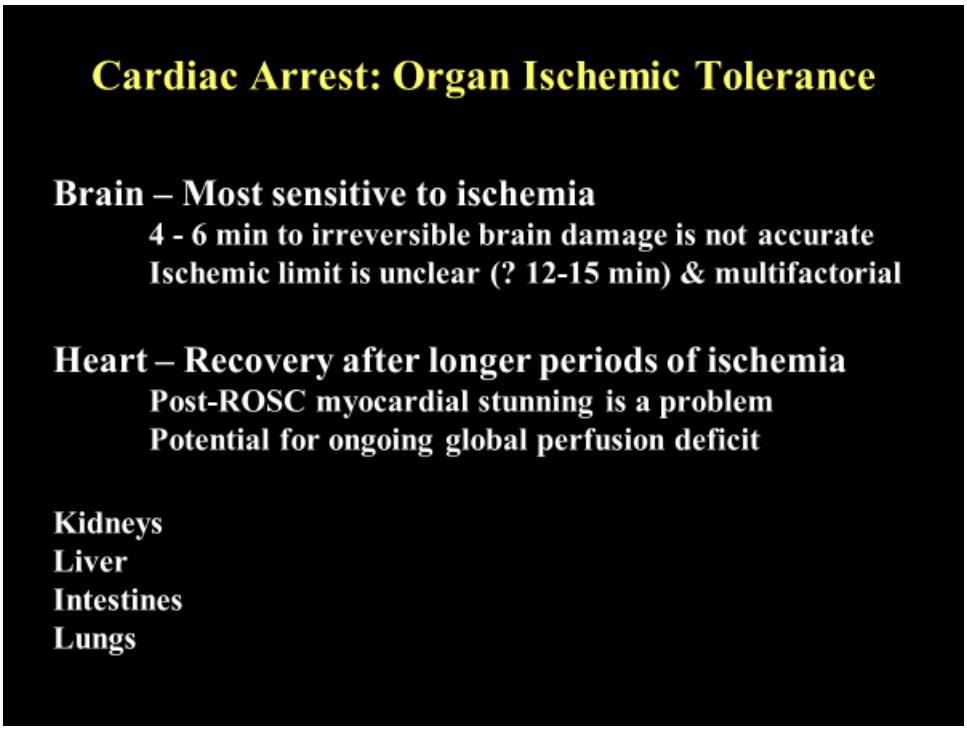
Activation of coagulation

Ischemic limits for Organs

The total burden of ischemia suffered by the organs in cardiac arrest is influenced not only by the initial time period of “no-flow” before resuscitation efforts are started but also by (1) any ischemic debt incurred between the initial acute physiologic insult and the onset of cardiac arrest, and (2) the degree of organ perfusion support generated by closed-chest CPR, a “low-flow” state. In general, shorter “no-flow” time, greater blood flow during the “low-flow” period of CPR, and shorter “low-flow” CPR time prior to achieving ROSC serve to limit the ischemic damage to the organs.

For many years the prevailing thought was that the brain, the organ most sensitive to hypoxic-ischemic damage, could only tolerate 4-6 minutes of ischemia before irreversible brain damage that precluded neurological recovery. Subsequent laboratory research and clinical observations indicate that good neurological recovery can be achieved after longer periods of ischemia, but there is substantial variation based on resuscitation, post-ROSC intensive care, individual variation and likely other factors that have not been well defined. Regardless, the shorter the ischemic insult, the better the chances of neurological recovery.

The myocardium can endure longer periods of ischemia than the brain, but functional recovery of the ischemic myocardium may be initially insufficient to allow for intrinsic cardiac perfusion without some mechanical assistance. Such myocardial stunning after the global ischemia of a cardiac arrest event may require extracorporeal perfusion support until the stunned myocardium can recover.



Global ischemia associated with cardiac arrest can lead to dysfunction in other organs. In general, if the global ischemia is of limited duration allowing for neurological recovery, most other previously healthy organs will also recover.

Medical (Non-Traumatic) Cardiac Arrest

As noted previously, Sudden Cardiac Death (SCD) is most commonly due to the abrupt onset of a ventricular dysrhythmia, either ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia. This can occur in people with no prior evidence of heart disease as well as people anywhere on the spectrum of severity for cardiac disorders. The volume status of the cardiac arrest victim is one of the factors that should be considered, and it is important to recognize that patients with heart disease may have a volume overload status prior to the acute event of a cardiac arrest. Thus, volume status can have implications for endovascular and extracorporeal perfusion support interventions during resuscitation.

Cardiac arrest can be caused by various acute events other than sudden cardiac death dysrhythmias. The cause of the cardiac arrest should be sought early in the resuscitation efforts since accurately identifying the underlying cause can significantly impact the course of action taken. Massive pulmonary embolism leading to cardiac arrest will likely require either thrombolytic therapy or interventional radiology procedure to achieve ROSC. Cardiac arrest due to pericardial tamponade requires pericardial decompression. Toxicologic causes of cardiac arrest may be amenable to pharmacological reversal or temporary extracorporeal perfusion support until the toxin is cleared or the effects have worn off.

Medical (Non-Traumatic) Cardiac Arrest

Sudden Cardiac Death

- Lethal Ventricular Dysrhythmia
  - Ventricular Fibrillation
  - Pulseless Ventricular Tachycardia

  - Associated with myocardial ischemia
  - Non-ischemic (Long QT syndrome)

Stable or no preceding physiological derangements

Favorable outcome if identified and treated promptly

Medical (Non-Traumatic) Cardiac Arrest

Rapid Progression – due to acute insults

- Severe Hypoxia
  - Airway obstruction
  - Overwhelming pulmonary infection
- Vascular Obstruction
  - Pulmonary Embolism
  - Pericardial Tamponade
- Cardiac Decompensation
  - Massive MI, acute CHF
- Pharmacologic/Toxicologic/Overdose
  - Beta-blockers, Calcium Channel Blockers

Hemorrhage-induced or Traumatic Cardiac Arrest

Acute severe, uncontrolled hemorrhage can rapidly lead to hypotensive hypovolemic hypoperfusion, cardiovascular collapse with impending cardiac arrest, and ultimately to true cardiac arrest. Although traumatic injures account for many such case of acute severe hemorrhage, non-traumatic causes of uncontrolled hemorrhage, such as gastrointestinal bleeding and obstetrical-gynecological catastrophes, can result in rapid exsanguination to cardiac arrest.

Hemorrhage-induced traumatic cardiac arrest (HiTCA) is the leading cause of death in both military and civilian trauma patients with otherwise survivable injuries. For this reason, substantial resources are being directed at early resuscitation and stabilization of trauma victims with uncontrolled hemorrhage. However, it is also important to be aware of and search for evidence of other traumatic injuries other than hemorrhage that can cause hemodynamic instability leading to cardiac arrest, including tension pneumothorax and pericardial tamponade.

The physiological response to acute hemorrhage proceeds along a continuum of derangement as intravascular hypovolemia and tissue hypoperfusion progressively worsen. Although blood pressure will drop some, compensatory mechanisms, including tachycardia, increase in systemic vascular resistance, and redistribution of blood flow centrally, engage to sustain vital organ perfusion. However, without cessation of hemorrhage and stabilization, this compensated shock state transitions into a decompensated shock state that ultimately leads to cardiovascular collapse (impending cardiac arrest) and then true cardiac arrest unless promptly reversed.

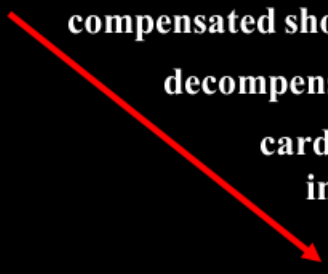
Hemorrhage-induced (Traumatic) Cardiac Arrest

Traumatic Hemorrhage (most common)
- Extremity – major vascular injury
- Non-compressible torso hemorrhage
  - Abdomen, Pelvis, Thorax – or combination
- (Blunt or penetrating mechanism)

Non-Traumatic Hemorrhage
- Gastrointestinal (variceal, ulcer)
- Aneurysmal rupture (AAA)
- Obstetrical catastrophe (uterine rupture)

Hemorrhage-induced (Traumatic) Cardiac Arrest

Acute severe hemorrhage
- intravascular hypovolemia
- tissue hypoperfusion – regional, then global
- hypotension
- tachycardia



- compensated shock
- decompensated shock
- cardiovascular collapse/ impending cardiac arrest
- true cardiac arrest

Closed-Chest Cardiopulmonary Resuscitation (CPR)

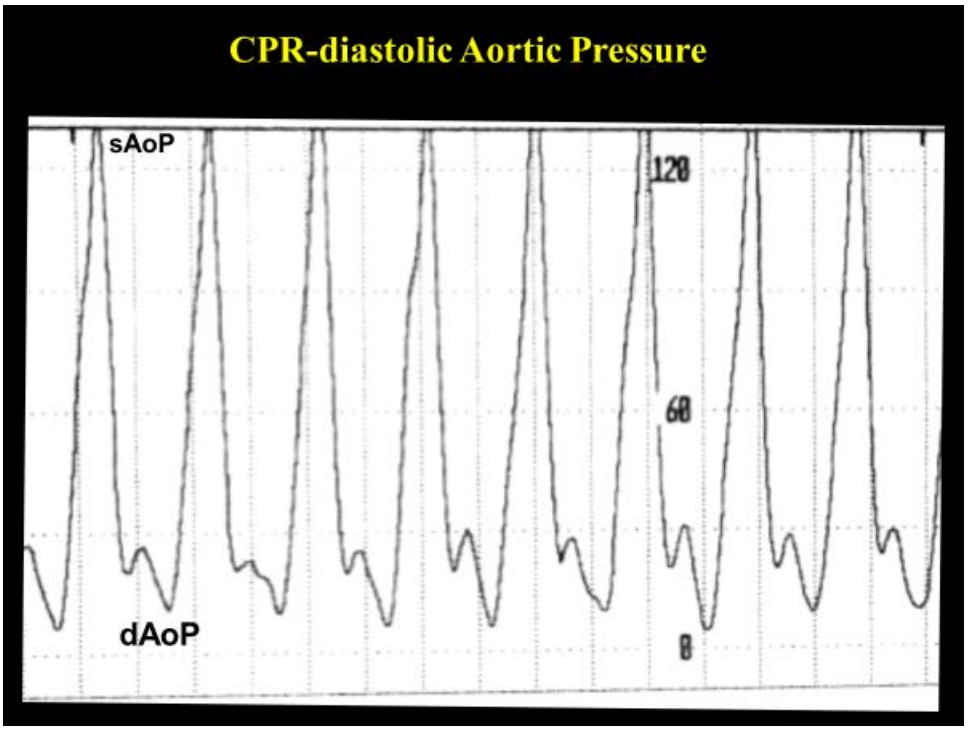
In a 1960 publication in JAMA, "Closed chest cardiac massage" was described. Since that landmark article, closed-chest CPR has been taught to millions of people throughout the world and is the basis for all subsequent resuscitation efforts.

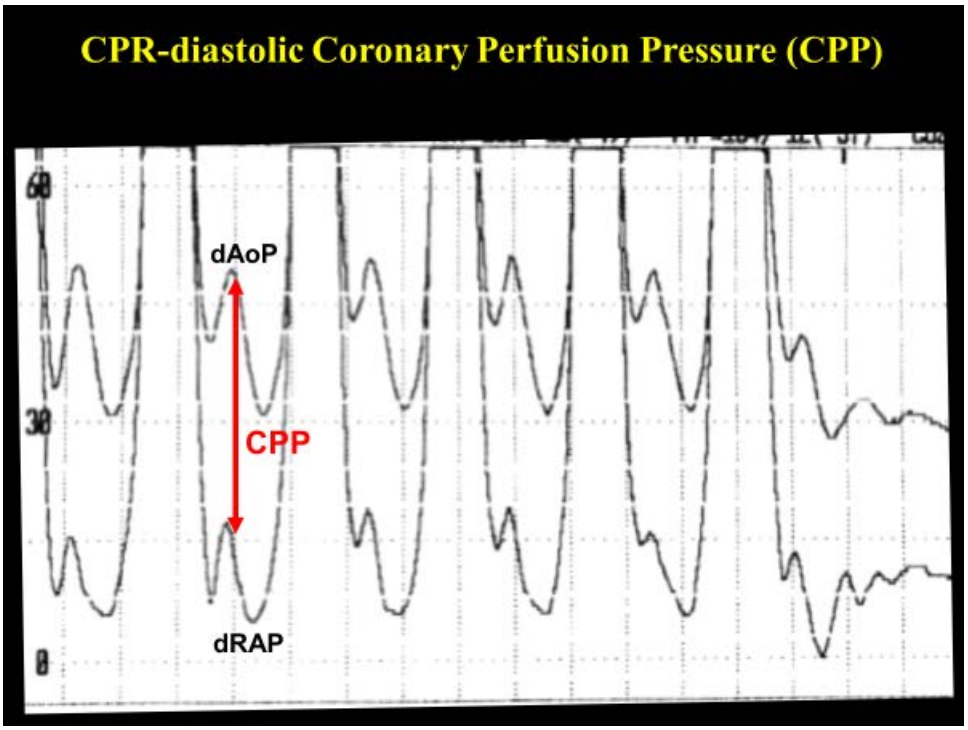
The mechanics of CPR have been the subject of extensive research and debate. Two fundamental mechanisms have been promulgated, the thoracic pump theory (blood flow is generated by intrathoracic pressure fluctuations) and the cardiac pump theory (blood flow is generated by compressing the cardiac ventricles). Regardless of the mechanism, or combination, it has been repeatedly shown that blood flow generated by closed-chest CPR is only a fraction of normal cardiac output. Yet, adequate myocardial perfusion with CPR is the key to achieving ROSC.

Both laboratory and human studies have shown that the driving force for blood flow during cardiac arrest is the "Coronary Perfusion Pressure" (CPP) defined as the aortic pressure minus the right atrial pressure during the relaxation phase of closed-chest CPR, also termed CPR-diastole. Preclinical and clinical studies show that a CPP of at least 15 mmHg is needed to provide enough blood flow to the heart to achieve ROSC, but the higher the CPP, the better the chances of ROSC. A major limitation of CPR is the decline in effectiveness with any time delay in initiating CPR, as well as, a decline in blood flow as CPR becomes prolonged; both related to progressive peripheral vasodilatation caused by tissue ischemia and acidosis.

Perfusion is the Key to ROSC.

CPP of at least 15 mm Hg is needed to achieve ROSC.


CPR-diastolic Aortic Pressure
sAoP
120
60
0
dAoP


CPR-diastolic Coronary Perfusion Pressure (CPP)
60
30
0
dAoP
CPP
dRAP

Pharmacology of Cardiac Arrest

The use of adrenergic agents and antiarrhythmic drugs to promote resuscitation from cardiac arrest has been a consistent part of standard resuscitation practice since shortly after the initial description of CPR.

The first-line resuscitation drug since for the past half century has been epinephrine. Extensive laboratory studies and clinical reports of human use in cardiac arrest have shown that epinephrine increases the rate of ROSC. The mechanism by which epinephrine improves ROSC is alpha-adrenergic vasoconstriction leading to an increase in CPR-diastolic aortic pressure during CPR. This increase in aortic pressure increases the CPP gradient previously mentioned and thus increases blood flow during CPR. However, the use of epinephrine during cardiac arrest has potential deleterious effects on perfusion of many vascular beds and oxygen delivery/consumption balance. Despite a half century of epinephrine use in cardiac arrest, there is no clear evidence that it improves long-term survival. Vasopressin has also been advocated for its more sustained vasoconstrictor effects during cardiac arrest, but likewise has never been shown to improve survival.

The use of antiarrhythmics in the setting of ventricular fibrillation has been recommended for several decades with lidocaine and amiodarone being the principal first-line antiarrhythmics. Laboratory studies and some clinical reports have demonstrated improved ROSC from refractory ventricular fibrillation, but no antiarrhythmic agent has been shown to improve long-term survival.

The major problem with pharmacological therapies in cardiac arrest is the poor circulation of drugs given intravenously such that they fail to reach effector sites.

Cardiac Arrest: Pharmacology

Vasoconstrictors – to increase CPR-diastolic AoP & CPP
- Epinephrine
- Vasopressin

Antiarrhythmics – refractory ventricular dysrhythmias
- Amiodarone
- Lidocaine

No pharmacologic agent has been clearly shown to improve long-term survival from cardiac arrest.

Cardiac Arrest: Pharmacology

Problem: During cardiac arrest & CPR, drugs given by an intravenous route are poorly circulated

Epinephrine – the most commonly given drug
- peripheral arterial vasoconstriction
- increase CPR-diastolic AoP & CPP
- increase blood flow to heart, brain, etc.

In the patients with the lowest CPR blood flow that need the epinephrine vasoconstrictor effect the most, the drug is circulated the least effectively

Dysrhythmias in Cardiac Arrest

Regardless of the path leading to it, the final common feature of true cardiac arrest is that the heart has stopped contracting and there is no forward blood flow. Although the EKG rhythm during cardiac arrest does not change this fact, a knowledge of the EKG rhythm or rhythms that have occurred with the acute insult can be very helpful in determining the etiology of the cardiac arrest and directing therapeutic decisions.

Ventricular fibrillation (VF) and pulseless ventricular tachycardia are the cardiac arrest rhythms commonly referred to as "sudden cardiac death" (SCD). These cause an abrupt loss of perfusion, generally without any preceding hypoperfusion or other physiological derangement from baseline. They are the rhythms most likely to respond to resuscitation and have a favorable outcome, particularly if early defibrillation is available. The lack of ischemia and acidosis prior to onset of cardiac arrest favors recovery if arrest is recognized early followed by prompt resuscitation. However, VF activity and lack of myocardial perfusion deplete ATP. Progressive ischemia and acidosis as cardiac arrest persists leads to a decrease in electrical energy or "coarseness" of the VF pattern (transition from coarse VF to fine VF) with associated lower likelihood for successful defibrillation and ROSC.

Asystole is often associated with a severe hypoxic-ischemic precipitating event or prolonged cardiac arrest, as does profound bradycardia or agonal rhythm.

Pulseless electrical activity (PEA) can be caused by various precipitating events, including massive pulmonary embolism, acute hemorrhage, pericardial tamponade and toxicologic exposures.

Cardiac Arrest: Dysrhythmias

Ventricular Dysrhythmias
- Ventricular fibrillation
- Pulseless ventricular tachycardia

Pulseless Electrical Activity (PEA)

Asystole / Bradyasystole (Agonal)

Survival rates are better for ventricular dysrhythmias than for PEA and asystole.

Cardiac Arrest: Dysrhythmias

"True" Cardiac Arrest
- Ventricular fibrillation
- Asystole
- PEA without cardiac contractions (EMD)

"Impending" Cardiac Arrest
- PEA with cardiac contractions (pseudo-EMD)

Monitoring CPR

A major limitation of present conventional resuscitation is the lack of adequate physiological monitoring capability to assess the adequacy of blood flow during closed-chest CPR. The presence of pulses with CPR does not correlate with blood flow because the blood pressure fluctuations are similar in both the arterial and venous systems. Pulses do not provide any information about the arterial-to-venous pressure gradient that generates blood flow.

The EKG has some qualitative value, particularly for ventricular fibrillation (VF) where a transition from a more fine (lower energy) VF waveform to a more coarse (higher energy) VF waveform is suggestive of improved myocardial perfusion. An increase in the rate of an organized rhythm also suggests some improvement in blood flow.

Continuous end-tidal carbon dioxide ($ETCO_2$) measurement is the most promising non-invasive measure readily available, but even this is at best a semi-quantitative guide to therapy and can be influenced by changes in minute ventilation and the use of vasoconstrictor drugs. Thus, there is no absolute $ETCO_2$ value that reflects adequate CPR blood flow. Some consider an of 10 mm Hg to be a minimum value indicating survivable CPR blood flow. In general, resuscitative efforts that increase the $ETCO_2$ likely indicate some improvement in CPR blood flow.

Emerging interest in the use of ultrasound and cerebral oximetry shows some promise. There is also increased use of arterial lines for pressure monitoring in some emergency departments and prehospital physician response systems.

Monitoring CPR & Resuscitation

Pulses

Pupils

EKG

End-Tidal Carbon Dioxide ($ETCO_2$)

Problem: None of these are accurate

- **$ETCO_2$ is the best of these but only semi-quantitative**

Ultrasound – useful qualitative information

Summary Slides

Cardiac Arrest Physiology: Summary

Cardiac Arrest can be abrupt in onset or rapidly develop after an acute insult

Abrupt: Sudden Cardiac Death
- Ventricular Fibrillation
- Pulseless Ventricular Tachycardia

Rapid: Response to acute insult
- Airway obstruction
- Pulmonary embolism
- Severe hemorrhage (traumatic, non-traumatic)

Cardiac Arrest Physiology: Summary

True cardiac arrest = heart stopped contracting

Impending cardiac arrest = heart still contracting, but no discernible blood pressure

Survival is worse in true cardiac arrest than impending cardiac arrest

Cardiac Arrest Resuscitation: Summary

Distinguishing "True vs. Impending" cardiac arrest has implications for resuscitation interventions

Closed-Chest CPR generates blood flow by creating a CPP gradient:

CPP = CPR-diastolic AoP – CPR-diastolic RAP

The effectiveness of CPR declines with time delay to initiation of CPR and with prolonged CPR

There is not a good non-invasive monitor for CPR blood flow

Cardiac Arrest Resuscitation: Summary

Resuscitation drugs given intravenous are poorly circulated during closed-chest CPR

Epinephrine – Increase in ROSC rate
No increase long-term survival

Early defibrillation for shockable rhythms improves long-term survival

Perfusion is key to achieving ROSC

END

Percutaneous and Surgical Vascular Access

Vascular access is the first step in any endovascular resuscitation technique. Therefore, it is imperative that practitioners of endovascular resuscitation be as knowledgeable and experienced as possible with both percutaneous and surgical vascular access techniques, For SAAP, this means initial femoral arterial access (right or left) for insertion of an appropriate size catheter introducer followed by insertion of the SAAP large-lumen balloon occlusion catheter.

Vascular access is not only the first step in any endovascular resuscitation procedure, but also the step with the greatest potential time variability. If arterial access can be achieved within a few minutes (1-5 min), rapid endovascular instrumentation and therapeutic interventions are possible. Therefore, the time required for initial vascular access significantly impacts resuscitation outcome.

Vascular access during emergencies is particularly challenging due to a variety of factors. The time urgency to initiate endovascular resuscitation limits flexibility for ultrasound (US) assessment of vascular anatomy, set-up, and procedural execution. Loss of pulses makes arterial localization difficult and ultrasound verification less apparent due to vasoconstriction and loss of pulsations. If CPR is being done, the movement presents an obvious additional challenge. Anatomical distortion such as a hematoma or edema can obscure ultrasound visualization. Vascular disease issues are magnified, and patient location can prove significant. Performing an endovascular procedure prehospital on the ground with potentially limited lighting is physically and technically more challenging than in-hospital.

Endovascular resuscitation interventions generally require femoral arterial, and sometimes venous, access [as noted in the slide at the bottom of the next page].

Vascular Access Challenges in Resuscitation

Cardiac Arrest or Impending Cardiac Arrest:

- Time urgency to achieve access
- Loss of palpable pulses
- Movement due to other interventions (CPR)
- Anatomical distortion (trauma)
- Vascular disease (atherosclerotic plaques)
- Patient location (floor, bed, prehospital)

Vascular Access for Endovascular Interventions

Endovascular Resuscitation:

Femoral vessels for catheter/cannula insertion

REBOA	femoral artery
SAAP	femoral artery (+/- vein)
V-A ECMO / ECPR	femoral artery & vein
Impella	femoral artery

EPR procedure presently via thoracotomy

Initial Vascular Access Strategy

Percutaneous access can be obtained either by using landmarks and blind insertion technique or, preferably in present day, by US-guided percutaneous access technique. Percutaneous access typically employs standard Seldinger technique with the needle-guidewire-catheter introducer kit that will allow for insertion of the endovascular resuscitation catheter. Alternatively, a mini-puncture technique can be used with a smaller needle and guidewire to initially place a smaller arterial catheter. This smaller catheter is then used for insertion of a larger guidewire and upsizing to the catheter introducer that will be required for the endovascular resuscitation catheter.

The mini-puncture technique might be optimally used to secure femoral arterial access in a hemorrhagic shock patient that may or may not ultimately need an endovascular resuscitation intervention. Securing vascular access while the patient still has a beating heart is generally easier, less time-pressured, and will save time later if endovascular resuscitation catheter placement is needed. Once cardiac arrest has occurred, the lack of pulsations and the vasoconstriction of the arteries makes femoral arterial access a more challenging task.

The initial insertion of a small femoral arterial catheter, by either standard or mini-puncture technique, allows for blood sampling for ABGs and continuous arterial pressure monitoring during the initial resuscitation phase which allows for more accurate & timely assessment of hemodynamic trends toward either stabilization or decompensation. If the patient stabilizes, this small arterial catheter can be removed and managed with direct pressure resulting in less risk of vascular access complications than the placement of a larger (i.e., introducer) catheter.

Percutaneous Vascular Access

Ultrasound-guidance:

Standard Introducer Kit

Mini-puncture Kit

The use of a mini-puncture or placement of a small catheter may be prudent in a patient of questionable hemodynamic stability:

blood for ABGs
continuous arterial BP monitoring

Percutaneous Vascular Access

Ultrasound-guidance:

Short Axis view (generally preferred), versus Long Axis

Stabilize US & needle hands

Approach vessel at about a 45° angle

Measure depth of the vessel (if vessel is 2-3 cm deep, needle skin stick should be about 3 cm caudally)

Continuously follow needle all the way down with US

Femoral Vascular Anatomy

Knowledge of pertinent femoral vascular anatomy is essential. The common femoral artery (CFA) at the inguinal ligament is positioned at approximately the midpoint between the anterior superior iliac spine (ASIS) and the ipsilateral pubic tubercle. Of note, the inguinal skin crease usually lies distal/caudal to the inguinal ligament. The CFA is lateral to the femoral vein and medial to the femoral nerve. The ilio-femoral vessels ascend from deep in the pelvis to their most superficial point as they pass over the pelvic brim and under the inguinal ligament before descending deeply again into the thigh. Thus, the course of the vessels forms an arc from the pelvis to the thigh and this has implications for the techniques used to obtain vascular access. Furthermore, the shape of this arc is variable.

For US-guided femoral arterial access, it is prudent to identify the CFA at the level of the inguinal ligament (at approximately the midpoint b/w the ASIS & pubic tubercle) and follow the CFA distally to identify the bifurcation into the superficial femoral artery (SFA) and profunda femoral artery (PFA).

The femoral artery should be accessed by needle insertion at the level of the CFA which lies between the inguinal ligament cephalad and the SFA/PFA bifurcation caudally. The concern for arterial puncture at or above (cephalad) to the level of the inguinal ligament is the risk of the needle passing through the posterior wall of the artery above the level of the pubic ramus. This area is not amenable to direct pressure and could result in non-compressible hemorrhage with retroperitoneal hematoma formation. This potential complication can be avoided with arterial puncture caudal to the inguinal ligament since this area is amenable to direct pressure hemorrhage control. It is also important to access the CFA rather than the

Anatomy

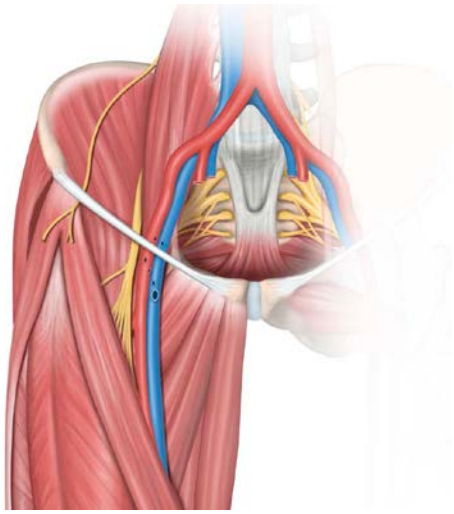
Surface Landmarks:

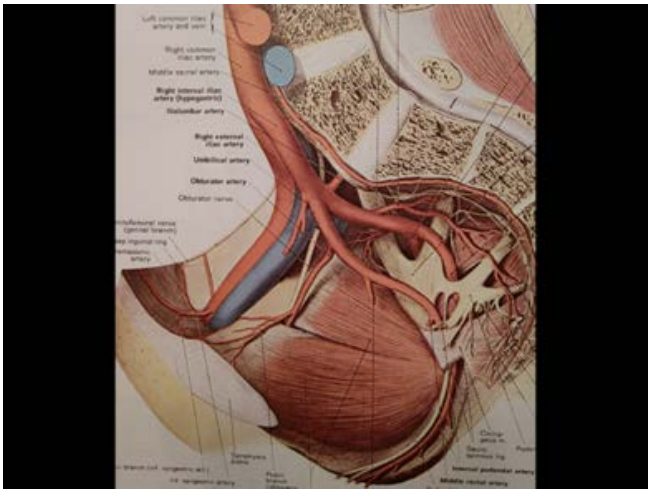
- Inguinal area landmarks – ASIS & pubic tubers
- Femoral artery crosses the inguinal ligament at midpoint b/w ASIS & pubic tubercle
- Inguinal skin crease lies a little inferior (caudal) to the inguinal ligament

Anatomy

Common Femoral Artery (CFA):

- Extends from the inguinal ligament to the bifurcation into the:
  - Superficial Femoral Artery (SFA)
  - Profunda Femoral Artery (PFA)
- Femoral vessels pass anteriorly over the pelvic brim at the medial aspect of the femoral head





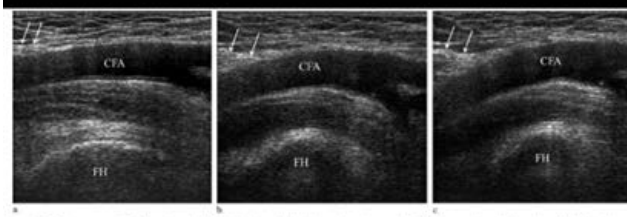
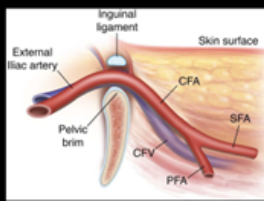


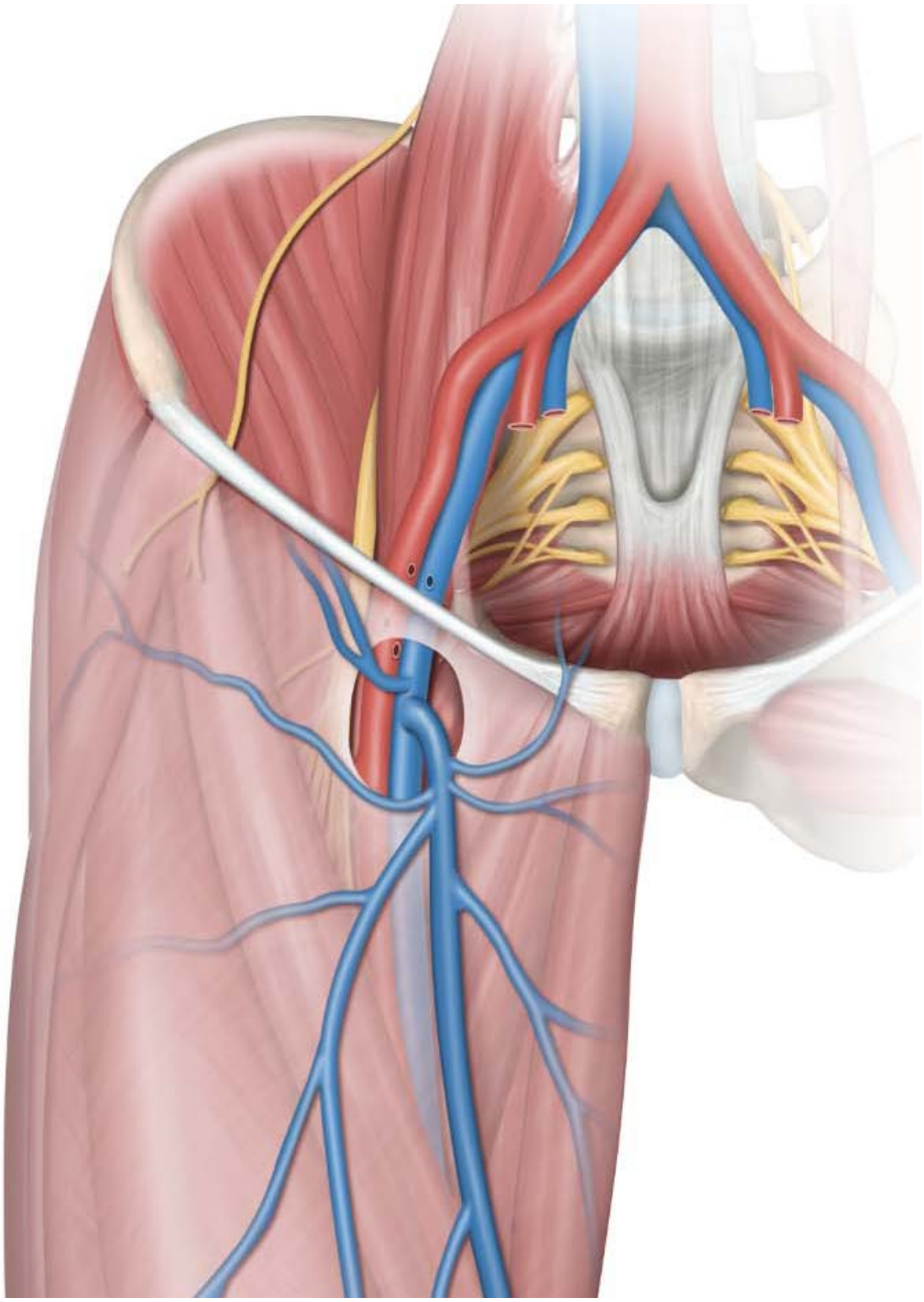
Figure 2. Three types of CFA on longitudinal US view. (a) In the horizontal type, the CFA is nearly parallel to the skin. (b) In the s type, the CFA is curved along the femoral head (*FH*). (c) In the slope type, the CFA is slanted forward more than 10°. US-ILs (arrows) also seen.

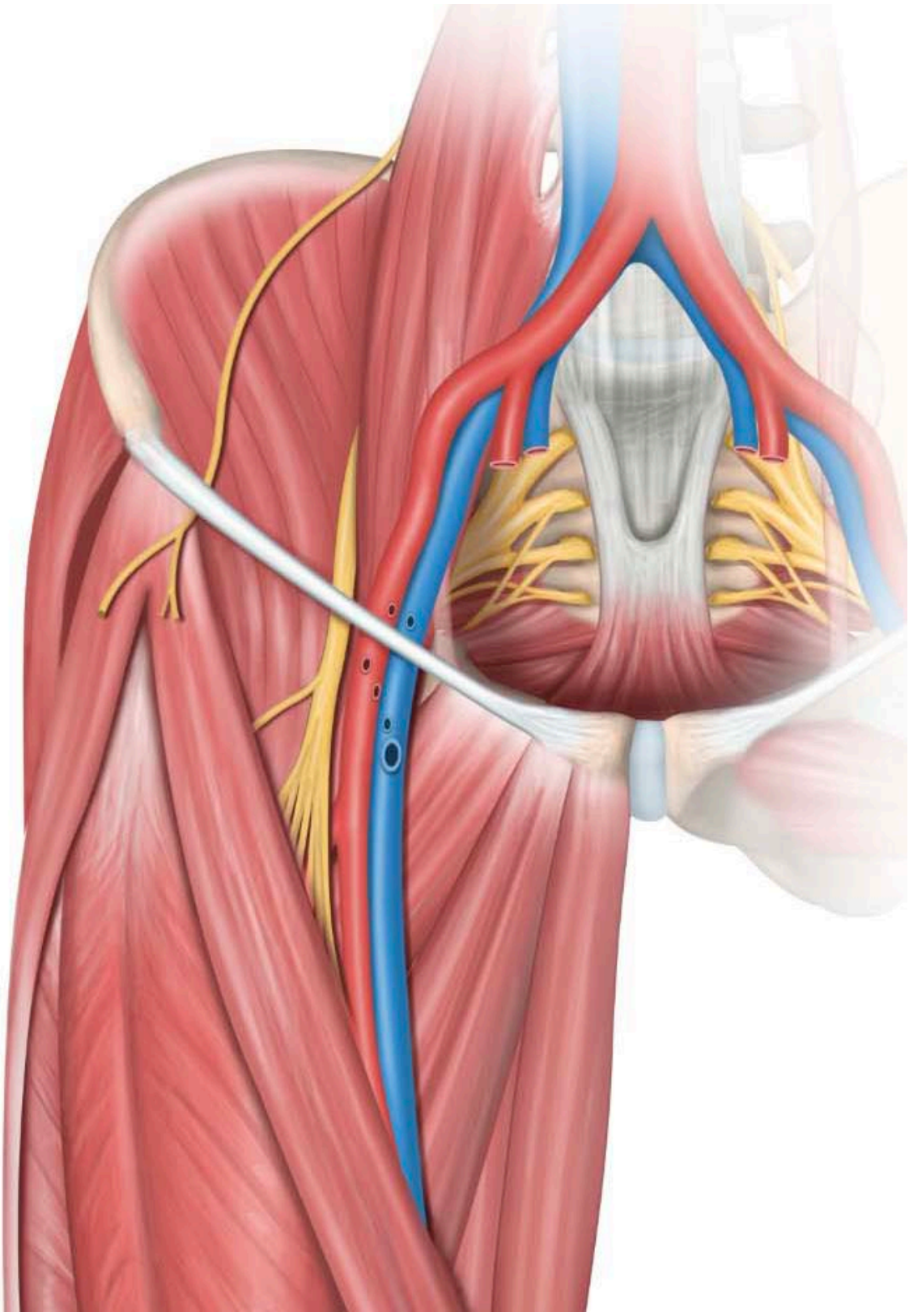
Anatomy

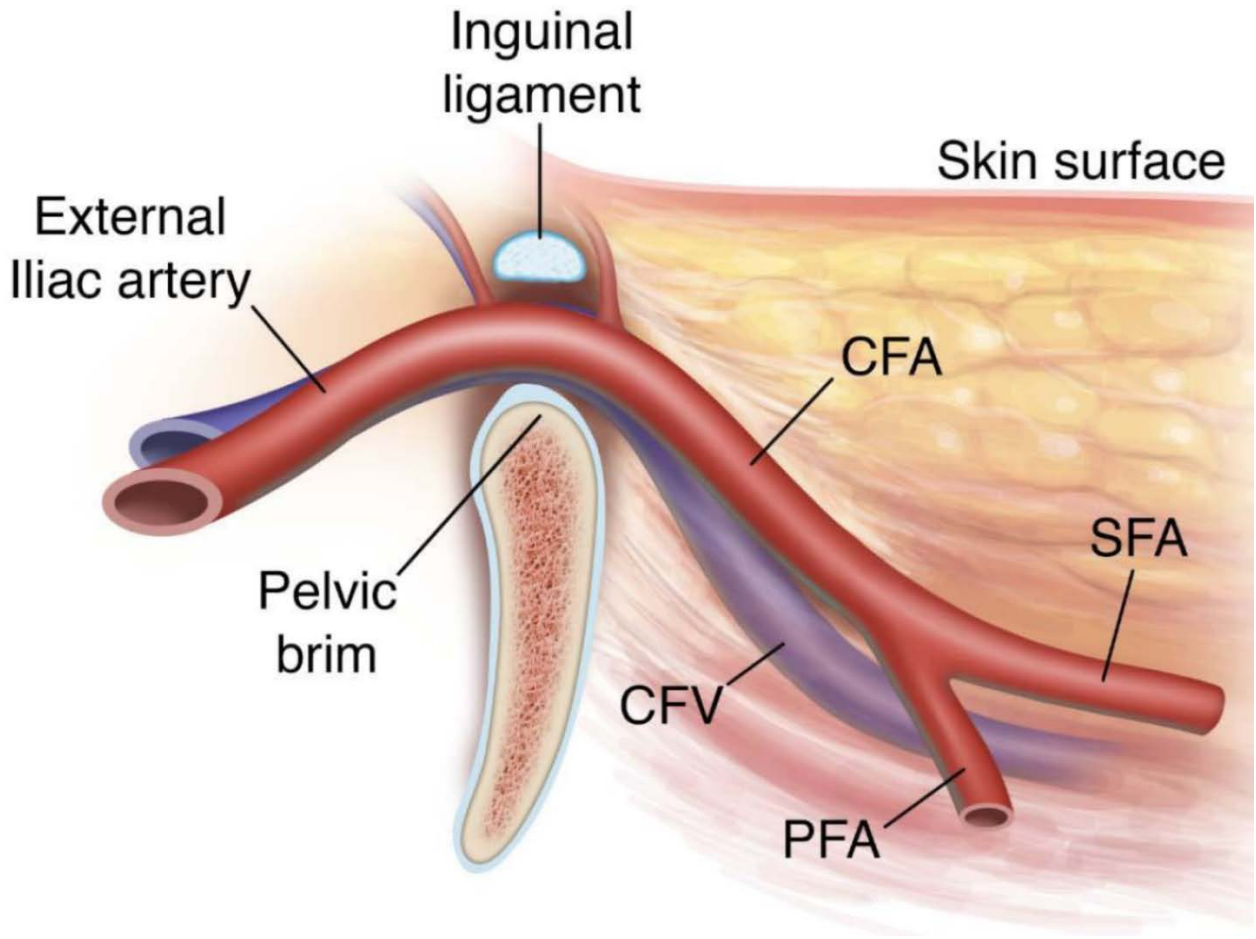
Common Femoral Artery (CFA):

- Femoral vessels pass from deep in the pelvis anteriorly over the pelvic brim (under the inguinal ligament), then back deep into the proximal thigh
- External Iliac – Common Femoral vessels' course forms an "arc" shape







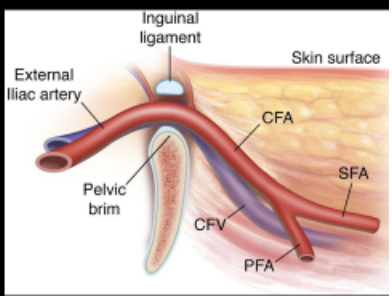


Anatomy

Common Femoral Artery (CFA):

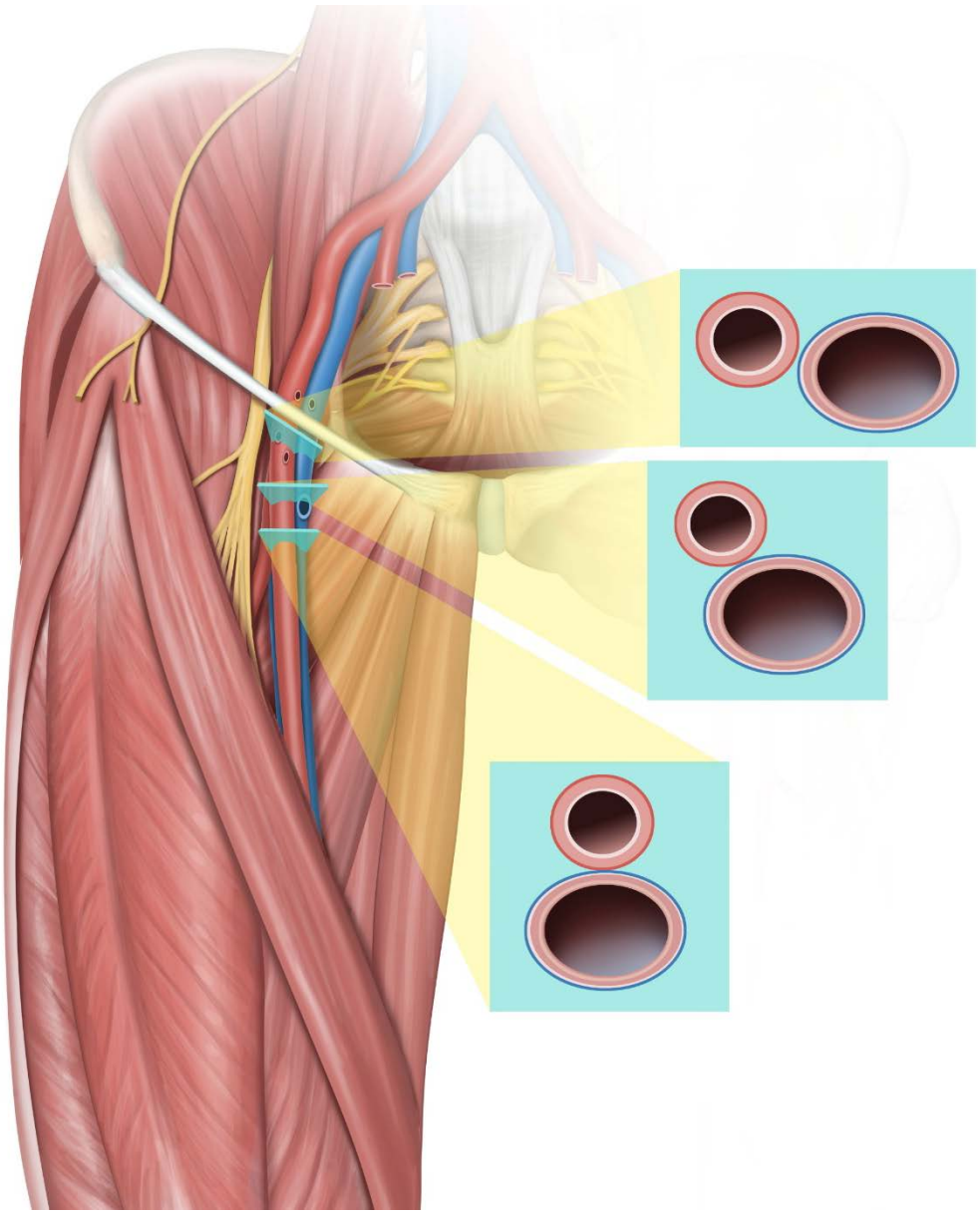
Femoral vessels pass from deep in the pelvis anteriorly over the pelvic brim (under the inguinal ligament), then back deep into the proximal thigh

External Iliac – Common Femoral vessels' course forms an "arc" shape



SFA to help limit the chances of distal vascular complications, such as thrombosis or compartment syndrome. At the CFA bifurcation, the SFA becomes smaller and the risk of SFA occlusion or thrombosis increases. The SFA supplies the distal leg, whereas the PFA does not extend distally to the same extent. The length of the CFA from the inguinal ligament to the SFA/PFA bifurcation may be as short as 3 cm or as long as about 6 cm. Thus, there is substantial individual variability. A study of 200 cardiac catheterization patients showed the average length of the CFA to be 4.3 cm. Therefore, it is prudent to try to identify the SFA/PFA bifurcation by US, if possible.

It is also important to recognize that the relative position of the femoral vessels changes as they progress more distally/caudally. At the inguinal ligament, the femoral artery is more consistently lateral to the femoral vein. However, as these vessels course into the thigh, they become deeper and the femoral vein tends to be in a more posterior (or dorsal) position relative to the femoral artery. From an anterior approach (by US or surgical cutdown), the femoral artery can be positioned directly on top of the femoral vein. This poses a challenge if access to both vessels is needed, such as, for V-A ECMO/ECLS. There is also the risk in a severe shock state or cardiac arrest of passing a needle through both the anterior and posterior walls of the femoral artery into the femoral vein. This can lead to the inadvertent insertion of the endovascular resuscitation catheter into the venous system (inferior vena cava) rather that into the arterial system (aorta). Such a misplacement of the endovascular resuscitation catheter would preclude the intended therapeutic effect and fail to improve the chance of ROSC or survival. Furthermore, it could potentially worsen the hemodynamic status of the patient, if not already in cardiac arrest.

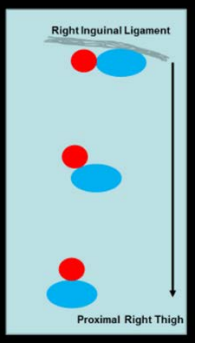


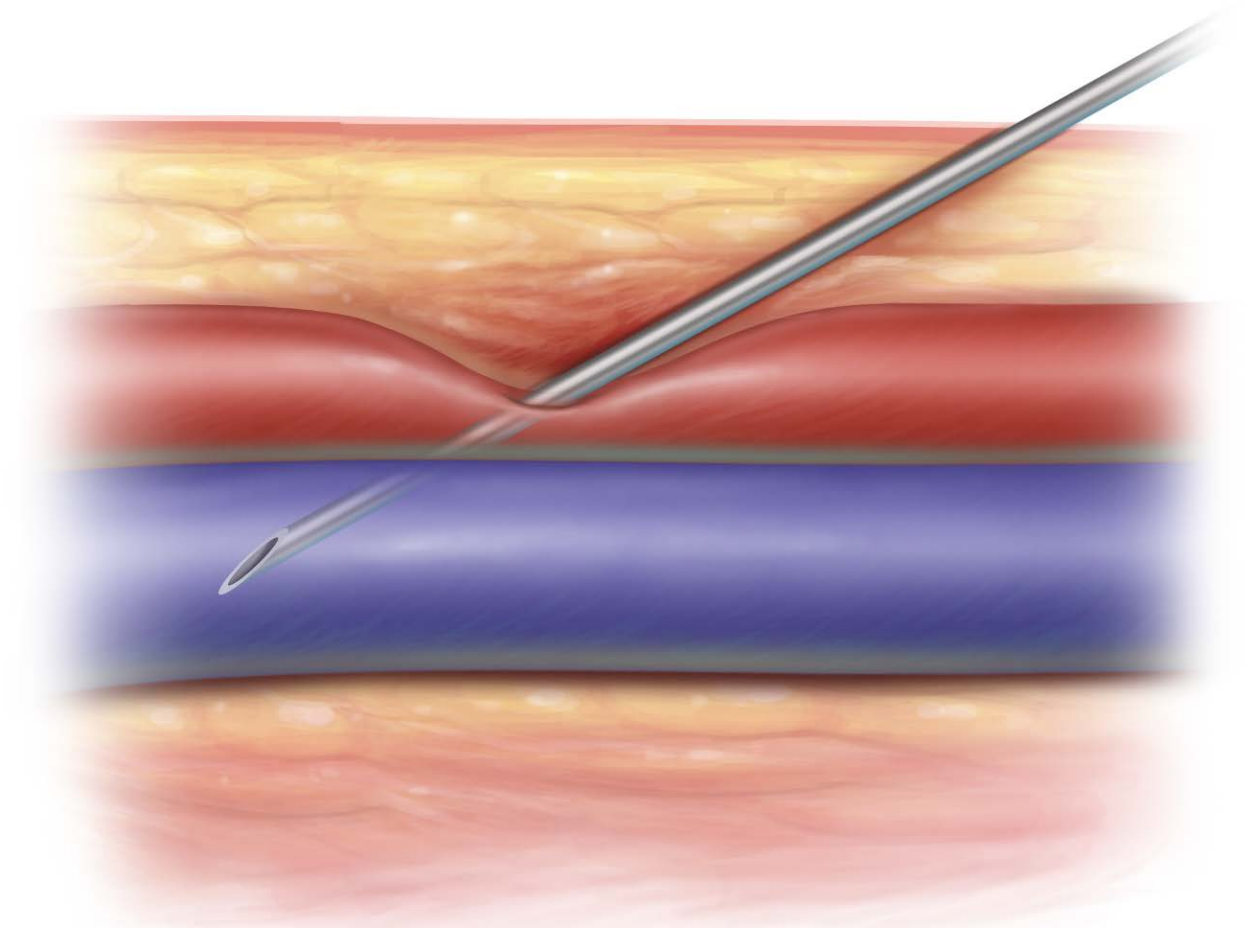
Anatomy

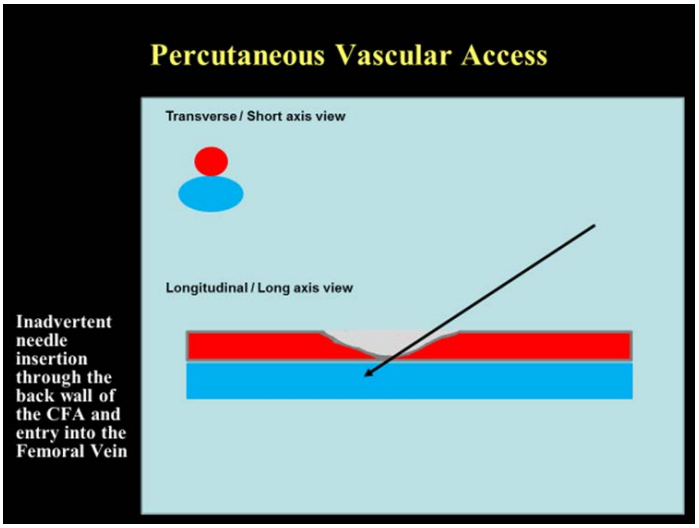
Shift in relative positions of the Femoral Artery & Vein:

The Femoral Artery typically moves from a lateral to a more anterior position relative to the Femoral Vein

(And again, the vessels also go deeper)





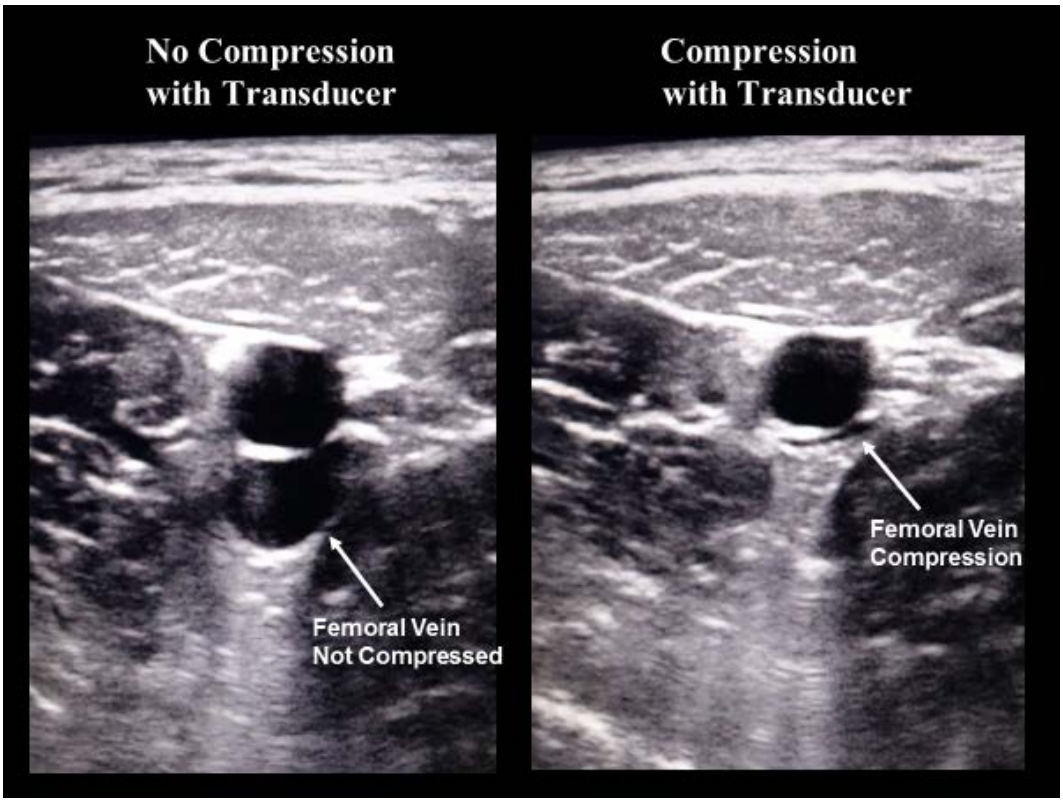

Percutaneous Vascular Access
Transverse / Short axis view
Longitudinal / Long axis view
Inadvertent needle insertion through the back wall of the CFA and entry into the Femoral Vein

Ultrasound identification of femoral vessels

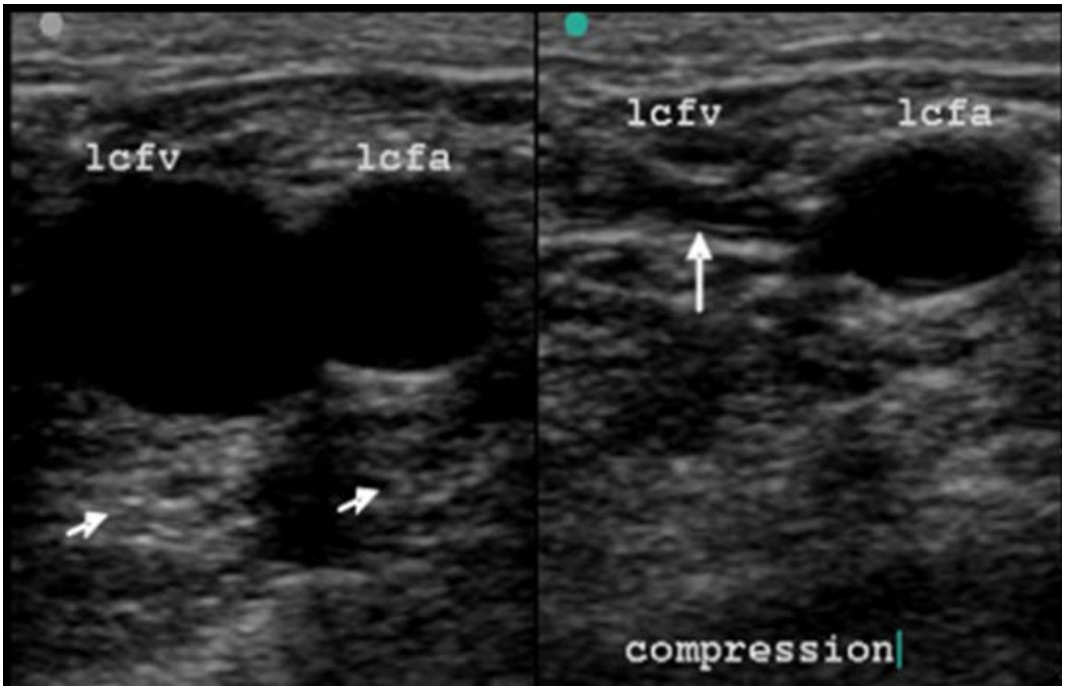
Distinguishing the femoral artery from the femoral vein is essential for endovascular resuscitation. Normally, the femoral artery is lateral to the femoral vein at the level of the inguinal ligament, but more distally the femoral artery tends to more anterior to the femoral vein, often overlying the vein when viewed by ultrasound from the anterior proximal thigh. Collapse of the femoral vein relative to the femoral artery with surface compression using the ultrasound probe is commonly used to help distinguish artery from vein. The intrinsic arterial pressure prevents arterial collapse with surface compression that easily collapses the vein. Compression of the femoral artery requires much greater surface compression force. The pulsations of the femoral artery also distinguish the femoral artery from the femoral vein during normal spontaneous cardiac contractions. In a cardiac arrest state, the arterial pulsations will be absent, and the arterial diameter will be smaller than during spontaneous cardiac activity due to vasoconstriction without any opposing distending pressure generated by the heart.

One of the challenges to femoral arterial access in true cardiac arrest or severe hemorrhagic shock with impending cardiac arrest is that the femoral artery will be vasoconstricted. The smaller diameter of the femoral artery makes percutaneous needle access & cannulation more difficult. In this situation US-guidance is particularly valuable since blind percutaneous needle insertion into a constricted femoral artery is much more difficult without US imaging. In cardiac arrest, there is equivalence of pressures waveforms in the arteries and veins with CPR chest compressions are being done. Thus, looking for pulsations during CPR to differentiate artery and vein is unreliable at best. The loss of normal arterial pressure can also make the arteries more collapsible with surface compression.

Porcine model showing femoral artery on top of the femoral vein



Human US image showing the Left Common Femoral Artery & Vein



Ultrasound-Guided Percutaneous Vascular Access

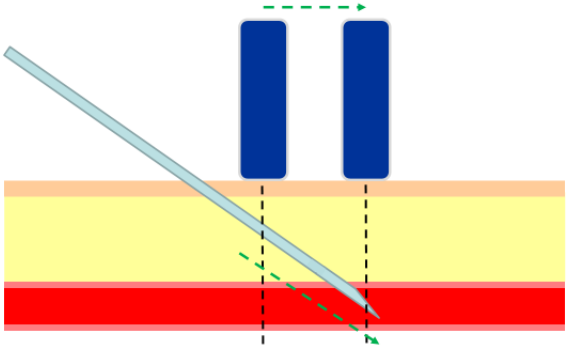
There are two fundamental US views used to guide percutaneous vascular access: (1) the transverse or short axis or out-of-plane view, and (2) the longitudinal or long axis or in-plane view. The choice of which view to use is the personal preference of the practitioner although most US experts recommend the transverse view for vascular access, particularly for those with less US experience.

The technique using the transverse view is to identify the vessel to be accessed and position the US probe such that the desired vessel is in the center of the image. The hollow tip of the needle is easily seen as a bright signal on the US image, whereas the needle shaft only creates a faint shadow that can be difficult to distinguish. The recommended technique is to follow the needle tip as it passes through the subcutaneous tissue until it enters the vessel. ***[The US probe is moved to follow and guide the needle tip toward the vessel.]*** This can be accomplished by either (1) sliding the US probe over the surface of the skin as the needle is being advanced, or (2) by rotating the US probe in an arc (sweep) with the surface contact point being held steady as the needle is advanced. Many experts recommend combined sliding and arc rotation/sweeping to follow the needle tip into the vessel and this combined technique is mastered with practice.

The technique using the longitudinal view involves identifying the desired vessel along the entire length of the US image and holding the US probe in a fixed position, so the vessel is constantly visible. The needle is then inserted and positioned so it remains in the plane of the US image as it passes through the soft tissue and into the vessel. ***[The US probed is stationary and the needle position is adjusted.]***

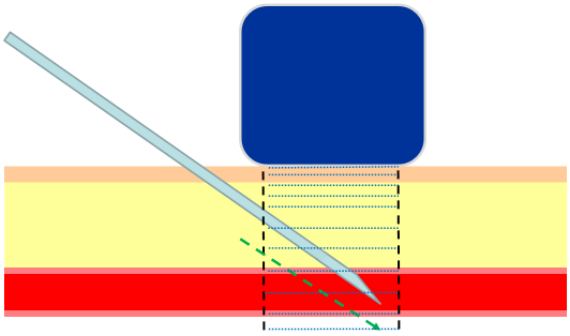
Ultrasound – guided percutaneous arterial access

Transverse (Out-of-plane) US View
Linear adjustment of the US Probe (Slide)



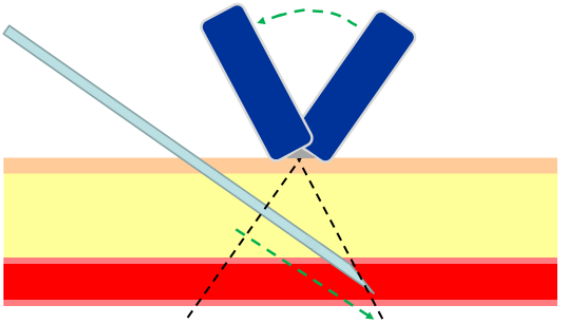
Ultrasound – guided percutaneous arterial access

Longitudinal (In-plane) US View
NO adjustment of the US Probe (Stationary)



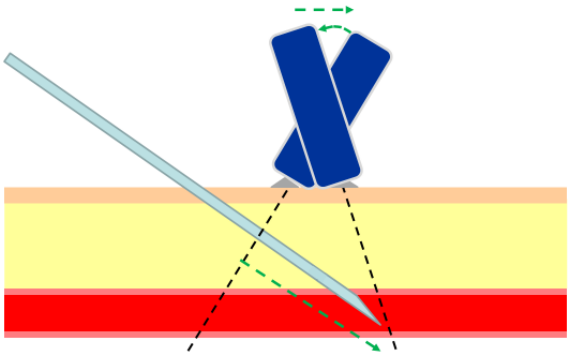
Ultrasound – guided percutaneous arterial access

Transverse (Out-of-plane) US View
Rotational adjustment of the US Probe (Sweep)

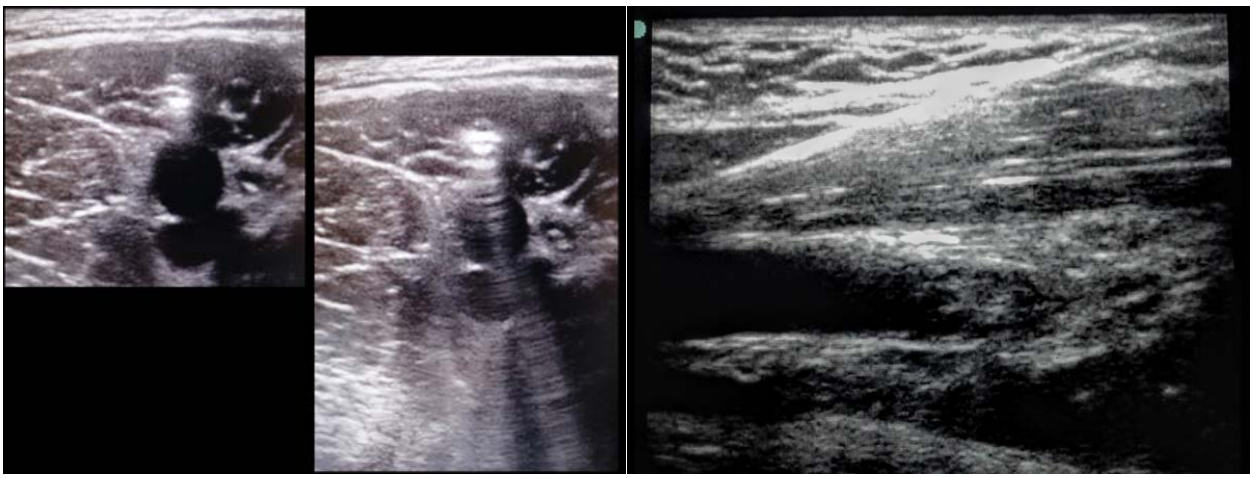


Ultrasound – guided percutaneous arterial access

Transverse (Out-of-plane) US View
Combined Linear & Rotational adjustment of the US Probe



Transverse (Out-of-plane or Short axis) View **Longitudinal (In-plane or Long Axis) View**



US experts often use both transverse and longitudinal views during a vascular access procedure. For example, the transverse view may be used for the initial insertion through the subcutaneous tissue until the needle is at the vessel wall and then switched to the longitudinal view to watch the needle pass into the vessel lumen.

Most US experts recommend inserting the needle at a 45^{o} angle from the plane of the vessel. The skin insertion point is chosen based on the depth of the intended vessel entry point. For example, if the vessel is 3 cm deep, the skin needle puncture should be 3-4 cm away from the US probe (caudally for femoral vessels) with the needle directed toward the center of the probe positioned such that the vessel is in the center of the US image. If using the transverse view, follow the needle tip and try to enter the vessel at its most superficial point (at the top or 12 o'clock position on the US image). If using the longitudinal view, position the US probe stationary with the vessel at its widest diameter along the entire course of the image and adjust the needle trajectory such that the needle tip remains clearly visible on the US image.

Some US experts recommend stabilizing both hands on the patient's body to help minimize unwanted movements that either alter the optimal direction of the needle or the optimal positioning of the US probe. Once the needle had entered the vessel, focus on holding the needle position very still and try to not take your eyes off the needle. This is when minor movements can cause the needle to be pulled out of the vessel or advanced through the posterior wall. Have the guidewire in the field so it can be retrieved without taking your eyes off the needle.

If the US image shows that the femoral artery is directly above the femoral vein, the relative position of the vessels may be improved by externally rotating the hip joint. This maneuver will tend to move the femoral artery into a more lateral position relative to the femoral vein. The US probe can also be moved medially a little bit. When the femoral artery is centered in the US image it will appear a little for lateral with this probe adjustment. This is also a situation where checking the needle position using the longitudinal US view may be helpful to assure that the needle is properly in the femoral artery and has not passed through the posterior femoral artery wall into the femoral vein.

Surgical Cutdown for Vascular Access

Surgical vascular access is one of the options for rapid femoral arterial and venous access in an emergency. However, it is not necessarily easy. It is important to understand the anatomy and practice surgical vascular access techniques (clinically, or on some model) as much as possible to be as facile as one can be with

the sequence of steps to find the femoral artery and efficiently insert the endovascular resuscitation catheter or cannula.

The first step in the surgical vascular access procedure is defining the location for and making the initial skin incision. This has more traditionally been performed by making a transverse incision that is roughly parallel and just distal to the inguinal ligament. However, vascular and trauma surgeons performing endovascular resuscitation interventions, such as REBOA or ECMO, in emergency situations are reporting the use of a longitudinal incision.

The transverse incision is generally, 2-3 cm below the inguinal ligament so that it will be directly over the CFA. The length of the incision needs to long enough to allow adequate visibility and maneuverability to allow for rapid dissection, identification and access to the femoral artery. This is typically a 6-8 cm incision to facilitate rapid and adequate exposure for arterial access. Although this is a long incision, it is in an area of lesser cosmetic concern.

The longitudinal incision more recently recommended is begun at the midpoint of the inguinal ligament and extended distally approximately 6-8 cm. The advantage of the longitudinal incision is the ability to extend the incision as needed if the initial incision does not allow adequate femoral vessel visualization. Cosmetic concerns are clearly secondary.

Surgical Vascular Access

Surgical Cutdown to the Femoral Artery:

Identify the Common Femoral Artery

(it may be possible to identify the bifurcation by seeing the PFA take off or from a tapering of the CFA to the SFA as the PFA takes off posteriorly…..potentially less noticeable in cardiac arrest)

The CFA should be accessed just proximal to the SFA / PFA bifurcation

Surgical Vascular Access

Surgical Cutdown to the Femoral Artery:

If the CFA in overlying the Femoral Vein, the risk of inadvertent insertion of a needle through the back wall of the artery into the vein still exists despite direct visualization by cutdown

(severe hypovolemia & cardiac arrest increase the risk)

Entering the artery from a medial or lateral angle can help prevent inadvertent entry into the femoral vein

The femoral vessels (as previously noted in the anatomy discussion) progress and move more deeply as they course from the inguinal ligament into the thigh. They will be deeper than one might initially expect, especially if there is a lot of overlying adipose tissue. The first large vessel that is encountered will likely be the greater saphenous vein. It is important not to mistake this for being the common femoral vein. It is necessary to dissect down through the overlying fascia and along the musculature to identify the neurovascular bundle that includes the femoral artery and vein. Again, as previously noted, at this level one may find that the femoral artery is ventral to (directly on top of) the femoral vein, or almost so.

Once the femoral artery and vein have been identified, needle puncture of the femoral artery and insertion of a guidewire can be performed in a manner generally consistent with standard percutaneous Seldinger technique. A direct femoral arteriotomy using a scalpel could also be performed, but this may be influenced by the size of the endovascular catheter or cannula that will be inserted. It is important to recognize that, if the femoral artery is overlying the femoral vein, it is certainly possible to pass a needle through the anterior and posterior walls of the femoral artery and then into the femoral vein, just as noted previously with percutaneous technique. Just because you have done a surgical cutdown to the femoral artery and are looking at it directly does not mean this inadvertent misplacement cannot occur.

Although the etiology of the cardiac arrest or shock/hemorrhagic shock episode leading to the true or impending cardiac arrest will influence the appearance of the blood, the color of the blood from the arterial puncture is still likely to have brighter red appearance than venous blood if the lungs have been functioning properly to oxygenate the blood passing through them up to the point of cardiac arrest or

impending cardiac arrest. However, if the etiology of the cardiac arrest involves acute hypoxemia related to some ventilatory failure (airway/pulmonary pathophysiology), the blood may be darker in appearance and not be distinguishable from the femoral venous blood.

If a femoral arteriotomy is performed directly with a scalpel, the size of the arteriotomy should be just large enough to allow insertion of the distal tapered end of the endovascular device dilator or obturator, such that when insertion of the final device will be sufficient snug within the artery as to avoid or minimize any blood leak around the endovascular device.

As with percutaneous technique when the femoral artery is overlying the femoral vein, the hip joint can be externally rotated to shift the artery & vein to a bit a more of a side-by-side position in an effort to help avoid inserting a needle through both walls of the artery and then into the vein. One technique is to approach needle puncture from the medial or lateral side of the femoral artery such that passing through the opposite wall of the artery will have the needle pass into the surrounding tissue and not into the femoral vein (this may or may not be visible, but would prevent aspiration or return of venous blood that could be mistaken for arterial blood).

If back bleeding occurs at the insertion site, packing with gauze would be the most appropriate temporary management. Placement of a suture tie or vascular loop around the femoral artery should not be done unless deemed absolutely necessary since this would render the leg ischemia. If done, it should be for the shortest time possible with clear recognition that this must be dealt with urgently.

As with percutaneous technique, the femoral artery should be entered at the level of the CFA proximal to the bifurcation. It may be possible to identify the

transition from the CFA to SFA at the bifurcation by a tapering of the vessel size (with the PFA taking off posteriorly and potentially not visible), but this transition in vessel diameter may be less noticeable in the hypovolemic or cardiac arrest state. For reasons as noted with percutaneous femoral arterial access, accessing the femoral artery more proximally at the level of the inguinal ligament is not advisable in order to avoid posterior arterial wall puncture above the level pubic ramus where hemorrhage cannot be controlled with direct pressure, thus risking a non-compressible retroperitoneal hemorrhage & hematoma.

"Hybrid" Technique for Vascular Access

The SAMU de Paris prehospital ECMO team uses a "hybrid" technique for femoral artery and vein access to initiate ECPR in the field. Used by the SAMU (or what they call a hybrid). This technique involves a surgical cutdown using a transverse incision with soft tissue dissection to identify the femoral vessels at the level of the CFA. Percutaneous needles are then passed through the skin on the distal/caudal side of the incision with direct visualization of the needle puncturing the artery or vein sequentially. With each needle puncture, an ECMO cannula guidewire is inserted followed by serial dilation steps before insertion of the ECMO cannulas. The incision is subsequently closed with no catheters passing through the incison. This technique could also be used for the placement of an introducer catheter for either REBOA or SAAP.

Choice of Vascular Access Approach

The choice of vascular access technique used is dependent on several factors, including: prior training and experience, available equipment, factors related to the specific patients body habitus, history of vascular disease, surgical history, and the environment where the procedure is being performed (prehospital or in-hospital). The endovascular resuscitationist should have facility with both percutaneous and surgical vascular access using the best technique for the presenting circumstances.

Website references for percutaneous vascular access and surgical vascular access in the swine skill lab sessions.

Website to view the Ultrasound vascular access video created by Tom Cook and Pat Hunt.

Hybrid Percutaneous – Surgical Vascular Access

SAMU de Paris:

Surgical cutdown to identify the femoral vessels

Percutaneous technique through the skin caudal (distal) to the skin incision

Needle insertion into the vessels under direct visualization

Skin incision is closed with standard techniques

Choice of Vascular Access Approach

Prior training

Prior experience

Equipment availability

Patient-specific reasons

Environment

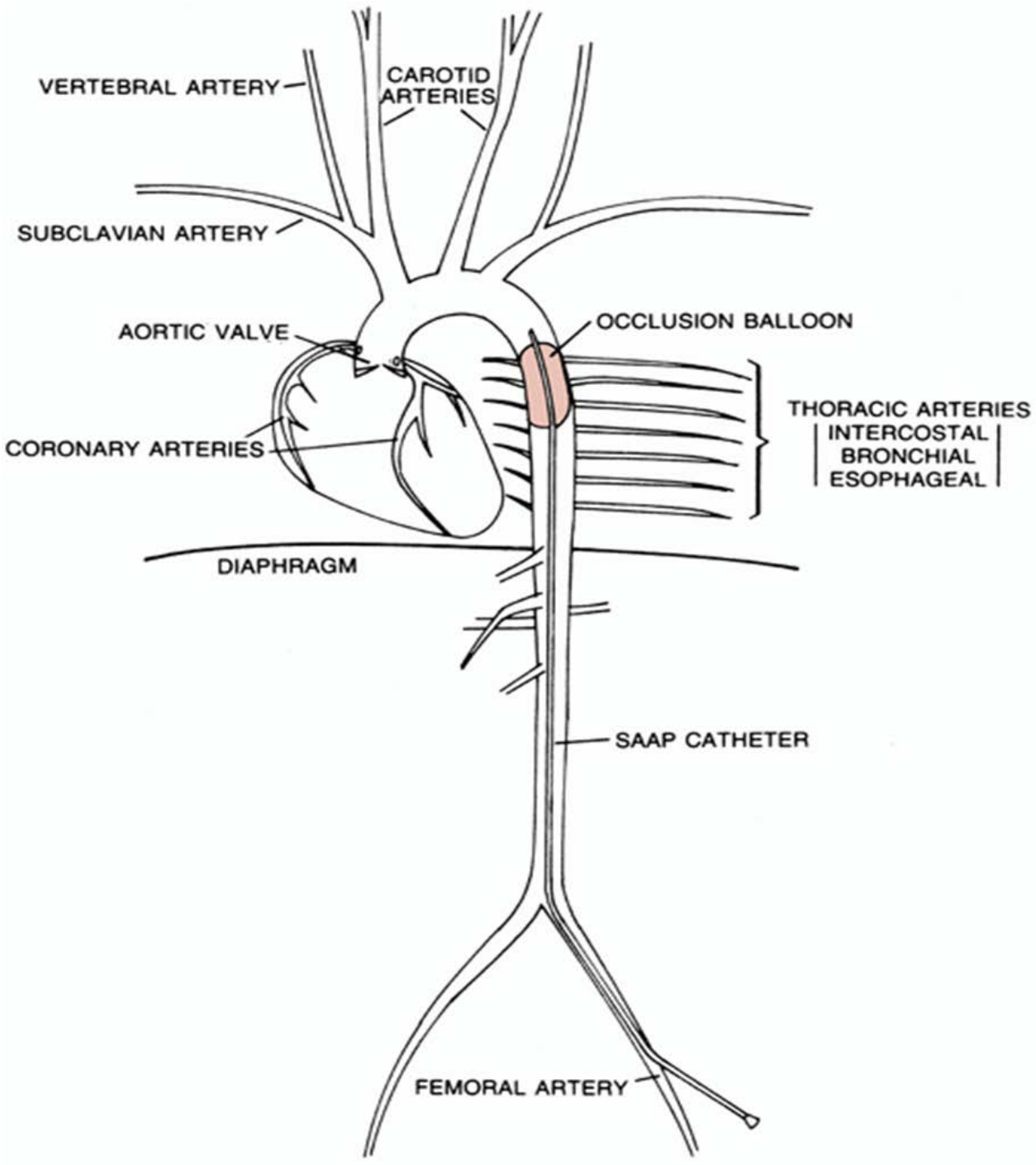
END

Selective Aortic Arch Perfusion (SAAP): Concept

Selective Aortic Arch Perfusion (SAAP) is an endovascular resuscitation technique that provides temporary extracorporeal perfusion to the heart and brain during cardiac arrest. The aim of SAAP is to reverse the cardiac arrest, resulting in restoration of intrinsic cardiac output with a palpable pulse, termed return of spontaneous circulation (ROSC), with a good neurological outcome. SAAP was developed specifically as a cardiac arrest therapy and is applicable to both medical cardiac arrest (sudden cardiac death) and hemorrhage-induced (including traumatic) cardiac arrest. The series of SAAP interventions (SAAP modalities) provides a stepwise escalation of aortic balloon occlusion and extracorporeal perfusion that generates higher blood flow than that achieved by closed-chest cardiopulmonary resuscitation (CPR). The sequence of SAAP modalities are used to achieve a ROSC, or to provide bridging heart and brain perfusion support until cannulation for prolonged veno-arterial extracorporeal life support (VA-ECLS) if required. These sequential SAAP modalities potentially allow for clearer diagnostic and therapeutic decision-making regarding resuscitation interventions in states of severe hemorrhagic shock and cardiac arrest. This chapter will describe SAAP and sequential escalating SAAP interventions, the rationale for SAAP in clinical practice, and how SAAP relates to other endovascular resuscitation techniques.

SAAP provides temporary extracorporeal perfusion to achieve ROSC in trauma & medical cardiac arrest.

Selective Aortic Arch Perfusion (SAAP)

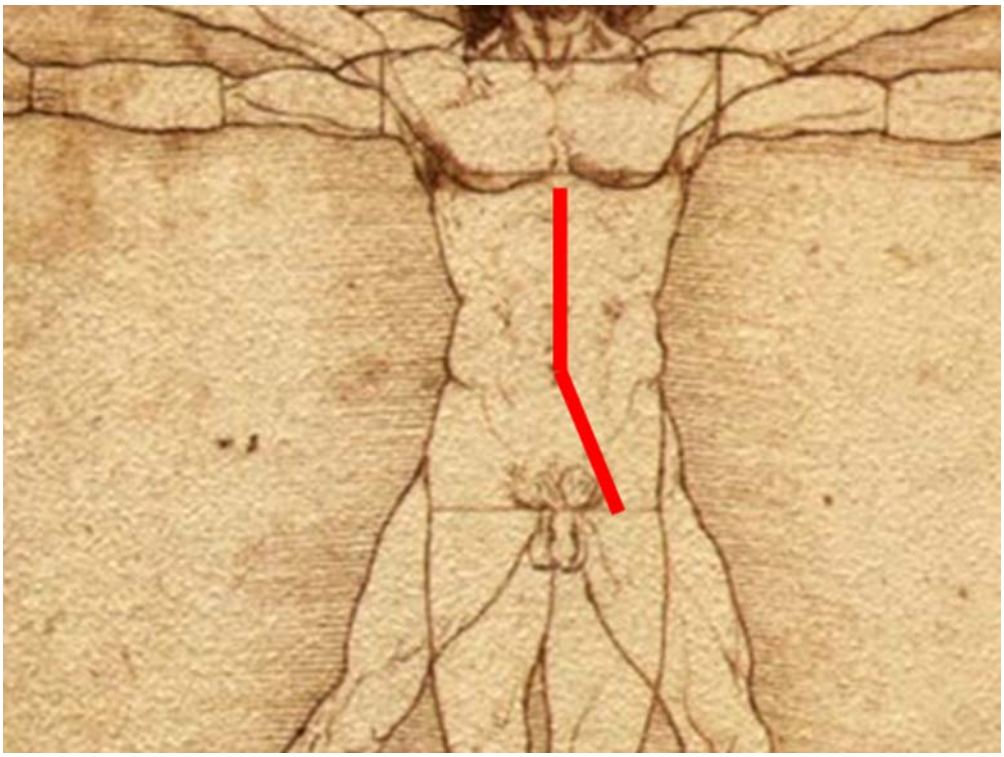


Description of SAAP

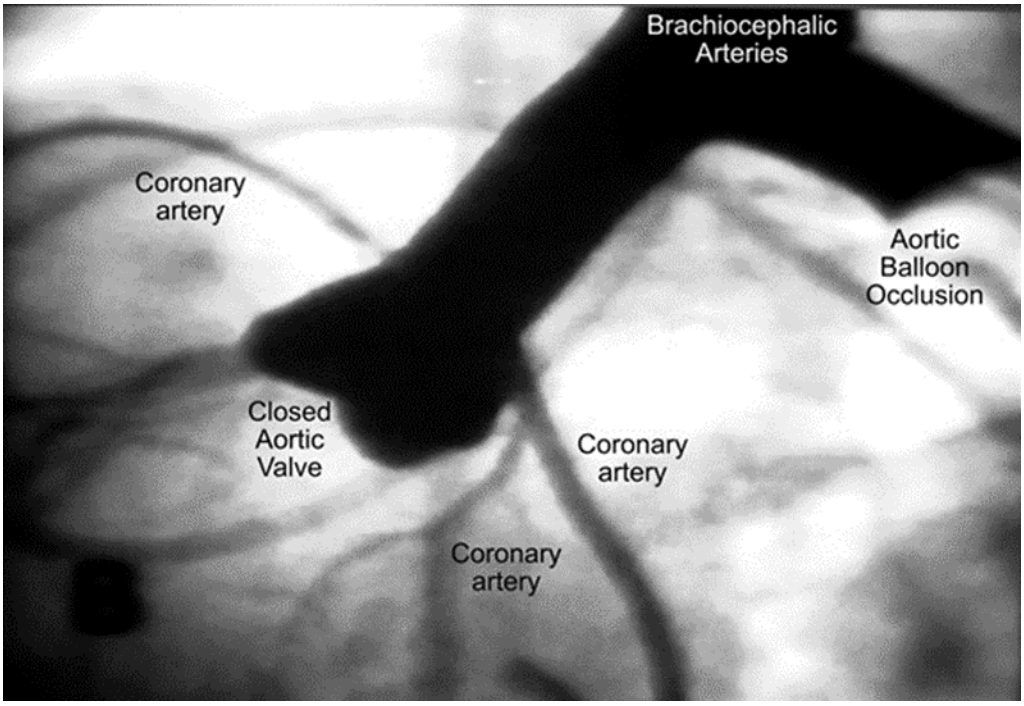
SAAP uses a large-lumen, balloon occlusion catheter inserted into a femoral artery and advanced to the level of the descending thoracic aorta with an insertion length based on body surface measurement (femoral insertion site-to-umbilicus-to-xyphisternal junction). This method positions the SAAP catheter balloon in the aorta between the diaphragm and the left subclavian artery. This leeway in balloon position within the descending thoracic aorta allows for insertion and initiation of resuscitative perfusion without the need for imaging technology to verify balloon location. When the SAAP catheter balloon is inflated, the aortic arch vessels, including the coronary, carotid, and vertebral arteries, are relatively isolated for perfusion with an oxygenated perfusate via the central infusion lumen of the SAAP catheter.

After the SAAP catheter balloon is inflated, an initial rapid bolus of perfusate (50 mL/two-three seconds) into the aortic arch is used to close the aortic valve, followed immediately by a steady infusion of perfusate to maintain aortic valve closure. This step is important, since failure to close the aortic valve can lead to regurgitation of the perfusate into the left ventricle, left atrium and pulmonary venous system limiting the beneficial effects of SAAP therapy in cardiac arrest. After the initial bolus, the infusion rate required to maintain closure of the aortic valve can be lower; 10 mL/kg/min has been used in most of the laboratory research studies to date. The key to maintaining competent aortic valve closure is that the subsequent infusion must begin immediately after the bolus, thereby not allowing the aortic pressure to drop and the aortic valve to open.

Body Surface Landmarks



Competent Aortic Valve Closure

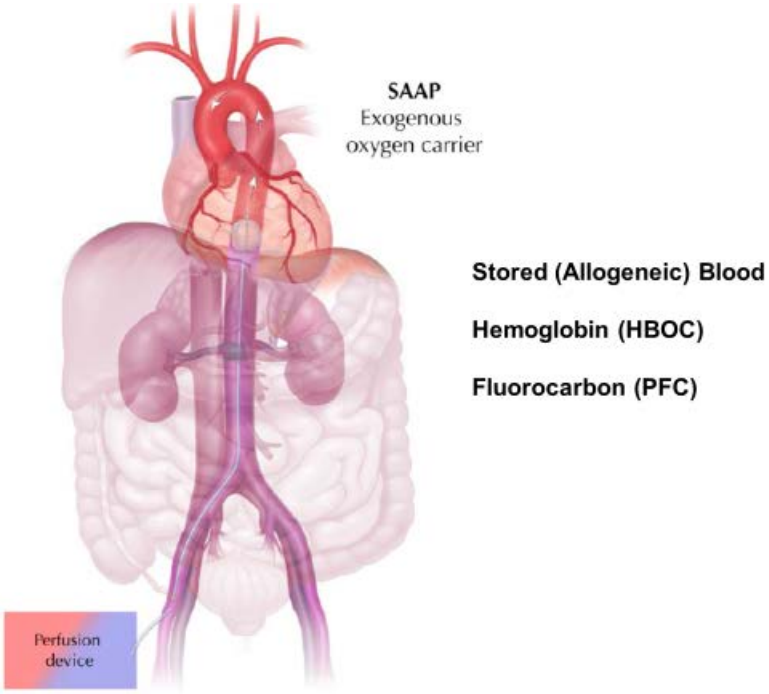


The initial perfusate is preferably an exogenous oxygen-carrier, such as stored (allogeneic) whole blood or packed red blood cells, or a non-blood product, such as a hemoglobin-based oxygen carrier (HBOC) or a perfluorocarbon (PFC) emulsion. The perfusate is passed through an oxygenator and infused using a pump system. Centrifugal pumps, roller-wheel pumps, and peristaltic pumps have all been used successfully to perform SAAP in laboratory models. Limited experiments to date have also shown that rapid serial boluses performed manually are also effective, but the overall perfusion rate is lower than mechanical pump continuous infusion and the time required to achieve ROSC is generally longer. Nonetheless, in austere environments - such as military theaters and some prehospital settings, manual infusion for SAAP may prove to be most practical.

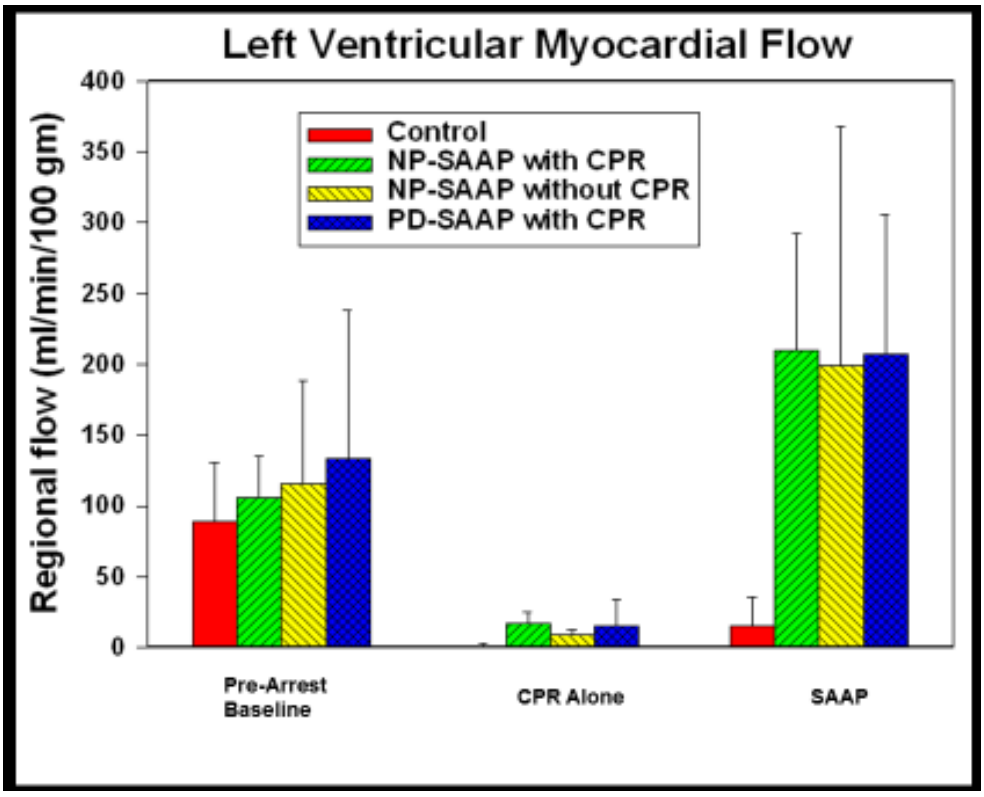
Myocardial blood flow during SAAP has been shown to not only be much greater that blood flow generated by closed-chest CPR, but to be even greater than during normal intrinsic beating of heart; that is, “supra-normal” blood flow. This is understandable based on the normal physiology of myocardial blood flow occurring during the diastolic phase of the cardiac cycle. For the heart in cardiac arrest, SAAP can provide continuous perfusion resulting in the supra-normal perfusion demonstrated by colored microsphere blood flow in preclinical laboratory studies.

SAAP begins with an exogenous oxygen carrier.
SAAP provides supra-normal blood flow to the heart.

SAAP Exogenous Oxygen Carrier



Myocardial Blood Flow during SAAP



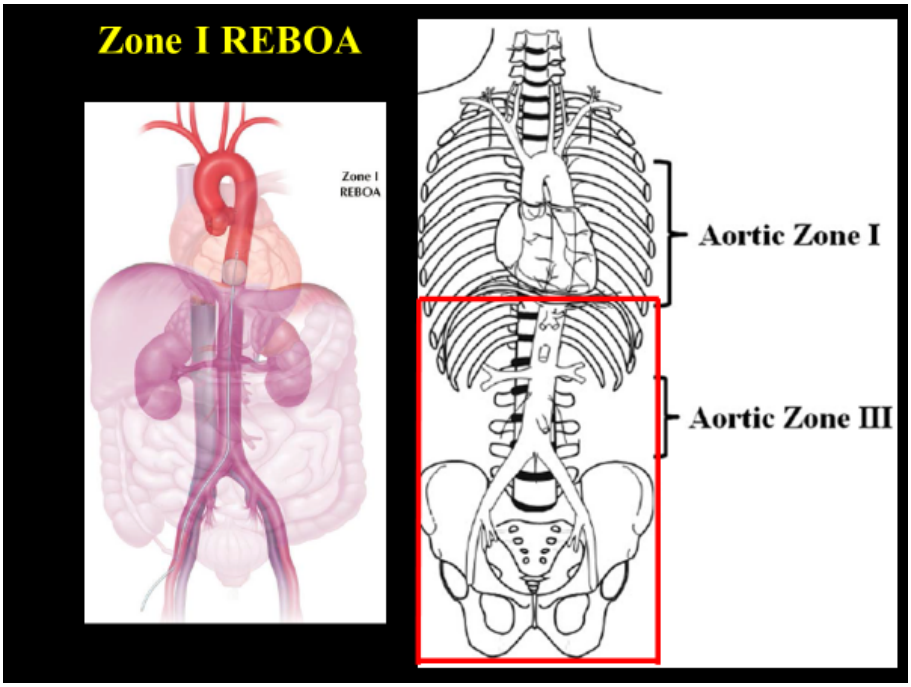
Comparison to Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA)

Looking at a diagram of SAAP, it looks much like a REBOA catheter. However, there is a fundamental difference between SAAP and REBOA. The names of the two techniques indicate the principle therapeutic intervention involved.

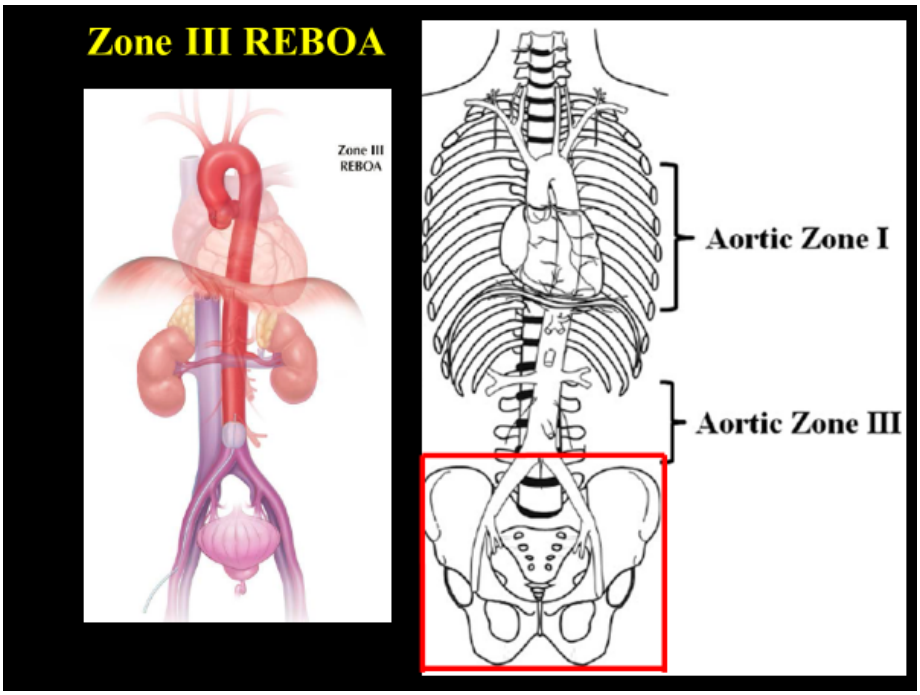
The therapeutic intervention of REBOA is “balloon occlusion of the aorta” for the purpose of achieving arterial hemorrhage control and supporting central mean arterial pressure cephalad to the inflated balloon. Perfusion cephalad to the REBOA catheter balloon is dependent on the actively beating heart. The increase in mean arterial pressure cephalad to the balloon is also dependent on spontaneous cardiac contractility. If a patient is in true cardiac arrest with no cardiac contractility, the inflation of the REBOA catheter balloon will not increase the central aortic pressure above the balloon and will not create myocardial perfusion alone. Closed-chest CPR is required with REBOA during true cardiac arrest to generate blood flow, and the effectiveness of CPR is known to be adversely affected by hypovolemia.

The therapeutic intervention of SAAP is “aortic arch perfusion” for the purpose of achieving ROSC and protecting the brain from ischemic damage. SAAP also serves as a route for administration of vasoactive drugs and pharmacologic agents to limit ischemia-reperfusion injury. SAAP does use an aortic balloon catheter, but the primary function of the inflated balloon is to limit the perfusion support to the aortic arch vessels, focused on heart and brain perfusion to achieve ROSC. Hemorrhage control caudal to the inflated SAAP catheter balloon, consistent with the function of a REBOA catheter, is a secondary benefit of the SAAP catheter in the presence of ongoing subdiaphragmatic hemorrhage.

Zone 1 REBOA



Zone 3 REBOA



Sequential SAAP Interventions

SAAP was developed specifically for the treatment of cardiac arrest and is applicable to both medical cardiac arrest and HiTCA. In medical cardiac arrest, the balloon occlusion isolates the flow of perfusate to the aortic arch (to preferentially achieve optimal heart and brain perfusion). SAAP also increases CPP, but this a secondary rather than primary effect. SAAP with an exogenous oxygenated perfusate is a volume loading intervention. Therefore, SAAP with exogenous perfusate is volume-limited (time-limited) intervention since it can lead to circulatory overload and result in pulmonary edema. In HiTCA, the volume loading by SAAP is actually beneficial as a means of rapidly restoring the intravascular volume loss associated with severe hemorrhage. If the major source of hemorrhage is subdiaphragmatic, the SAAP catheter balloon inflated in the thoracic aorta serves to limit further arterial hemorrhage caudal to the balloon in the same way as Zone 1 (thoracic aortic) REBOA. However, the principal aim of SAAP with exogenous perfusate is to provide heart and brain perfusion to achieve ROSC just as in medical cardiac arrest. The immediate need to achieve ROSC in HiTCA means that SAAP is not contraindicated in the setting of intrathoracic hemorrhage even if it may lead to additional bleeding. However, the effectiveness of SAAP may be more limited with thoracic trauma, depending on the vascular injuries and the rate of bleeding.

Clinical decision making in endovascular resuscitation

Endovascular resuscitation is not without risk to the patient. In the early management of medical cardiac arrest and hemorrhagic shock, the benefit:risk of ECPR and REBOA, respectively, are not well understood. In traumatic hemorrhage, this clinical dilemma is best illustrated by the clinical decision-making around which patients require REBOA in order to survive to the operating theater for definitive

surgical hemostasis and which patients will survive to surgical hemostasis without REBOA and its potential risks. Identifying the patients that will rapidly progress to a state of impending cardiac arrest (heart still beating but no discernible blood pressure) leading to true cardiac arrest (heart no longer contracting) is a significant challenge. In medical cardiac arrest, the optimal time for initiation of V-A ECLS/ECPR after standard therapies have failed remains unclear and is likely variable on an individual patient basis. ECPR followed by extended post-ROSC VA-ECLS can lead to complications and potentially burden ICU services.

Whilst it is expected that more advanced intervention (for example, SAAP compared to REBOA) confers a greater potential risk to the patient, it is also more likely to result in a ROSC and a good outcome and can be used when the risk:benefit is clearer. SAAP modalities may present a neat solution to help navigate this theoretical dilemma, via their logical, sequential, escalating (both in terms of intervention level and risk) perfusion interventions. The ability to sequentially escalate interventions, as needed, based on the patient's response to therapy has the potential to clarify the risk:benefit decision-making process of endovascular intervention. The aim of this escalation is to achieve ROSC as rapidly as possible with the fewest resources and the lowest risk to the patient, whilst providing vital brain perfusion.

Sequential escalating SAAP interventions

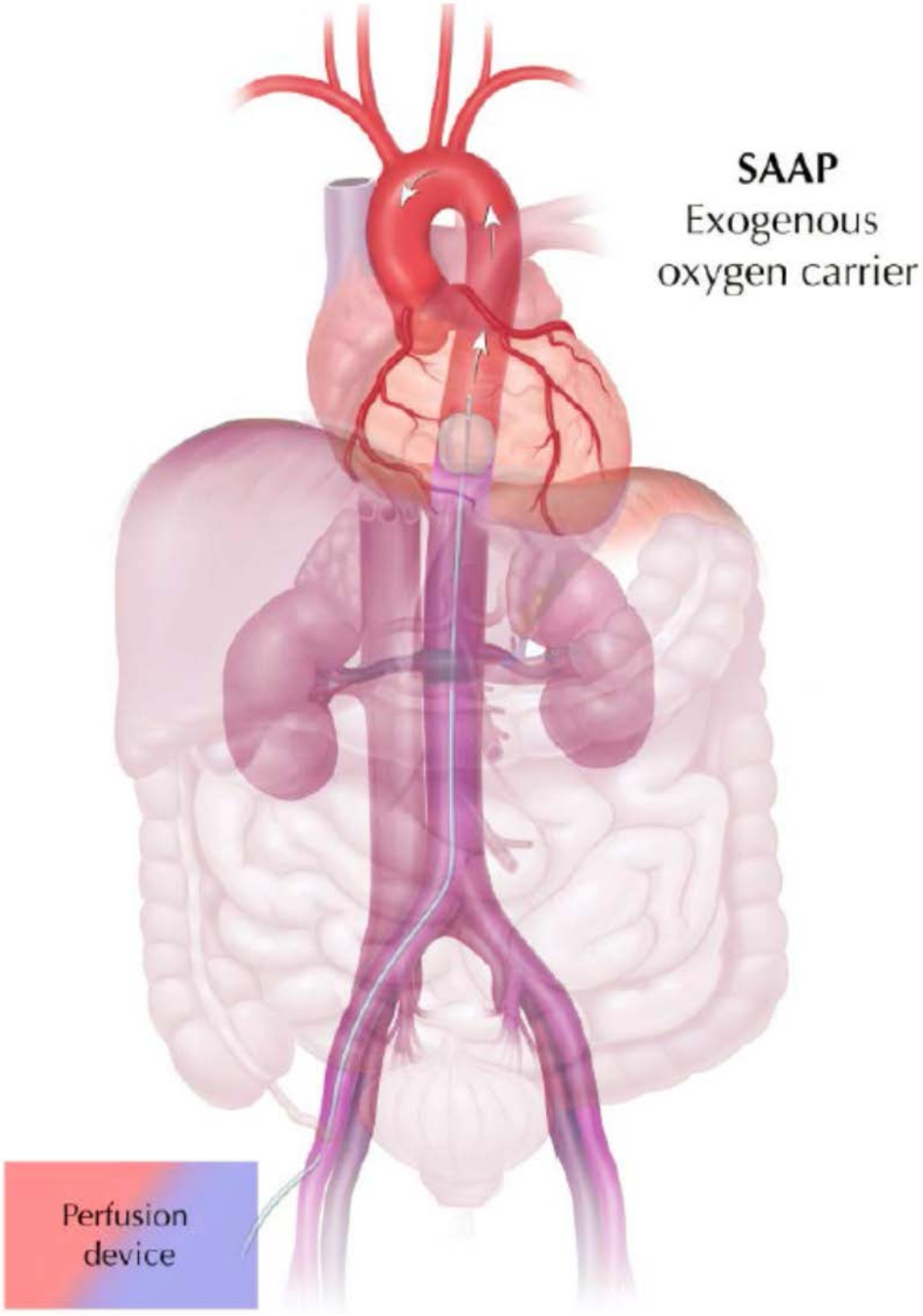
The use of sequential SAAP interventions and the timing of deflation of the SAAP catheter balloon will vary depending on whether the cause is medical cardiac arrest or HiTCA. There are three perfusion support modalities that can be employed using the SAAP catheter leading ultimately to transition to VA-ECLS, if needed.

SAAP with an oxygenated exogenous oxygen-carrier

The initial SAAP intervention allows for rapid initiation of heart and brain perfusion because it only requires femoral arterial access and insertion of the SAAP catheter to begin perfusion support. Stored (allogeneic) whole blood, diluted allogeneic packed red blood cells, hemoglobin-based oxygen carrier (HBOC), and fluorocarbon emulsion (PFC) are potential exogenous oxygen-carriers; all of these have been studied as SAAP perfusates with favorable results. The use of whole blood or packed red blood cells with standard citrate anticoagulant requires the concomitant administration of calcium mixed with the blood product in a proportion to normalize the ionized calcium just before infusion via the SAAP catheter. This must be done accurately. An HBOC in a balanced salt solution, such as HBOC-201, does not require concomitant calcium. The administration of epinephrine during this initial SAAP phase may be beneficial for its peripheral vasoconstrictor effects or for its inotropic effects. SAAP with an exogenous oxygen-carrier is a volume-loading intervention and the duration of this modality depends upon the volume status of the patient at the time of cardiac arrest.

In HiTCA, SAAP with exogenous perfusate can continue until ROSC and normal intravascular volume has been restored. With continuous SAAP infusion this could be four to six minutes or longer depending on the total blood volume lost, the presence of ongoing hemorrhage, and the volume of exogenous perfusate available. Once ROSC and volume recovery have been achieved, the SAAP infusion is stopped, but can quickly be re-started if required. The deflation of the SAAP catheter balloon is dependent upon the presence or absence of ongoing hemorrhage caudal to the inflated balloon. If hemorrhage control is needed, the

SAAP Initial Perfusion Phase

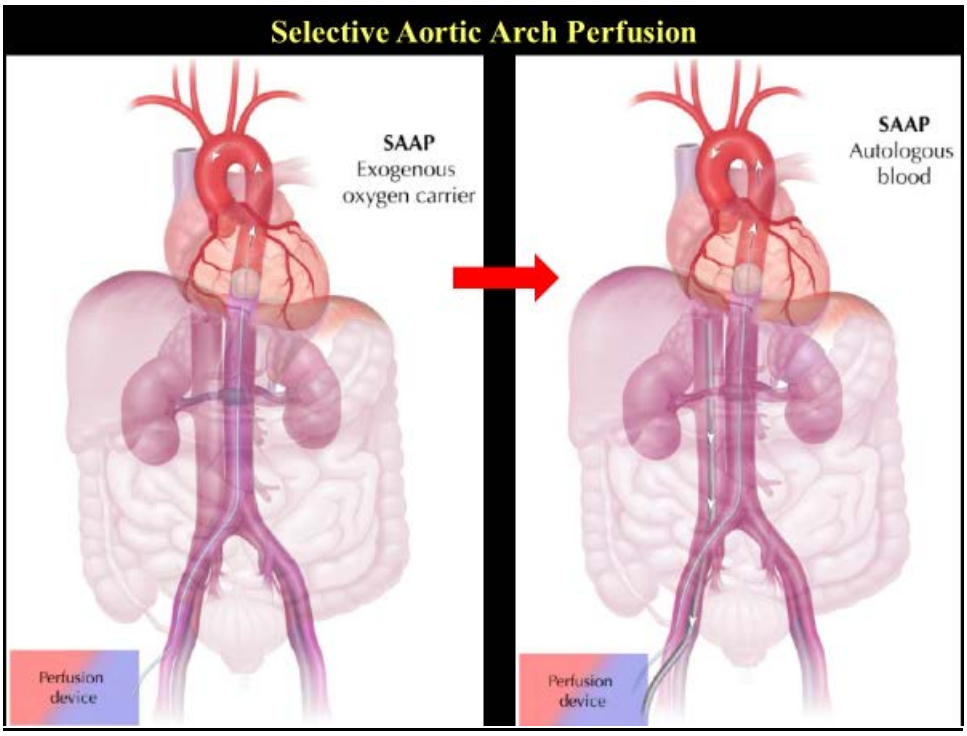


SAAP catheter balloon can remain inflated, serving to function as Zone 1 REBOA. However, the time limit for SAAP catheter balloon inflation should probably be no longer than 30 minutes. The shorter time limit than that recommended for REBOA is necessary owing to the expected ischemic burden from the physiological insult of HiTCA as compared to severe hemorrhagic shock. The cumulative ischemia time for the abdominal viscera includes the cardiac arrest time period plus the balloon occlusion time. Thus, SAAP balloon occlusion time in HiTCA needs to be shorter than for Zone 1 REBOA.

For medical cardiac arrest without hypovolemia, SAAP with exogenous perfusate will likely be more time limited. This SAAP modality can be used for up to about four minutes before transition to the next modality. If this SAAP modality is used intermittently (for example, SAAP for one-minute alternating with CPR for one to two minutes), this phase can be extended to about eight to ten minutes. During this initial SAAP with exogenous oxygen-carrier intervention, femoral venous access should be obtained to allow for transition to the next SAAP modality if ROSC has not been achieved or post-ROSC hemodynamics are not sufficiently stable. If ROSC occurs during initial SAAP with exogenous perfusate and there is a stable post-ROSC intrinsic perfusion and arterial blood pressure, the SAAP catheter can be flushed with crystalloid (to prevent clot formation and allow further use) and the SAAP catheter balloon deflated. As soon as hemodynamic stability is achieved, the SAAP catheter can be removed.

Sequential transition through the SAAP modalities is used, only if needed, to achieve ROSC and stability.

Sequential SAAP Modalities



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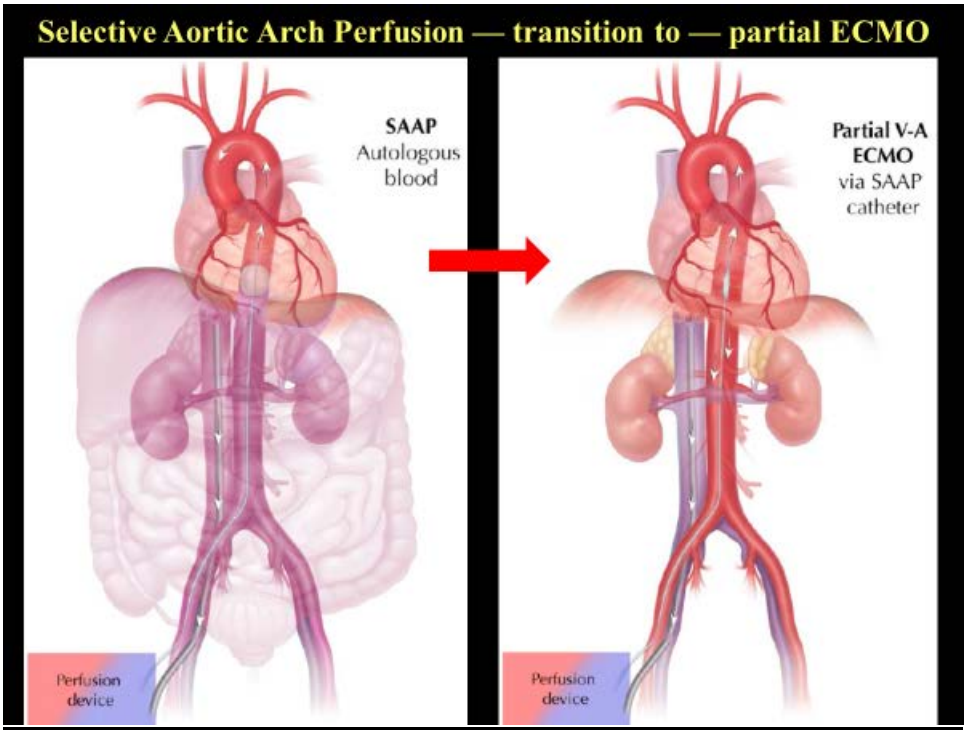
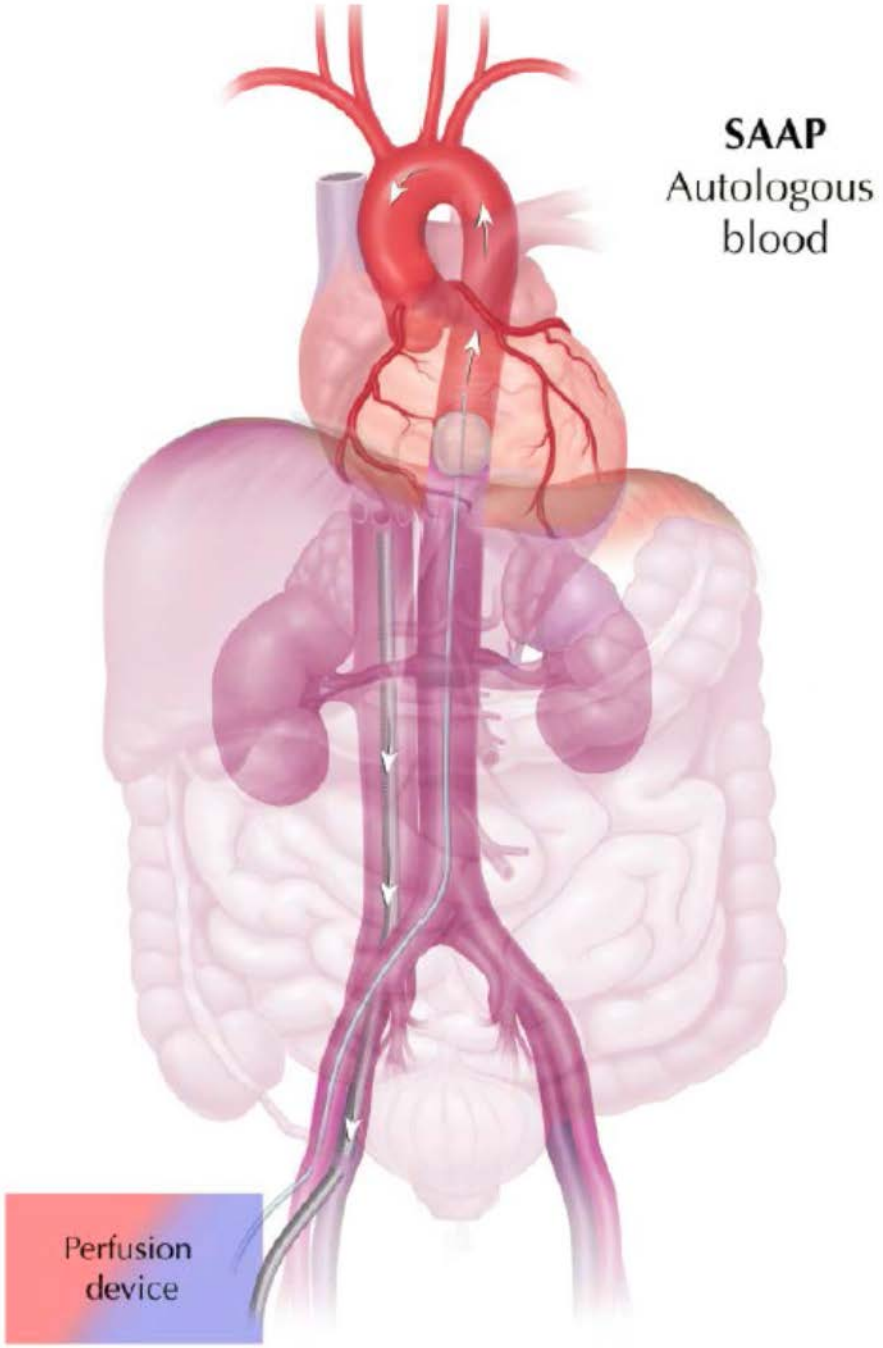


SAAP with oxygenated autologous blood

The second SAAP modality requires femoral venous catheter access in order to withdraw the patient's autologous blood to continue SAAP therapy using a closed veno-arterial circuit. Therefore, in anticipation of the need for this SAAP modality, femoral venous access is obtained during the initial SAAP exogenous perfusate phase. The autologous blood is circulated through an oxygenator and pumped back into the aortic arch via the SAAP catheter with the balloon still inflated. The benefits and risks of heparin anticoagulation should be considered at this point and may be influenced by the cause of cardiac arrest and the availability of heparin-bonded circuits. Since there is no further volume loading with this modality, it can be continued for a longer time period. The SAAP with oxygenated autologous blood modality is most likely to be used in medical cardiac arrest victims in whom initial SAAP exogenous perfusate was time-limited and additional extracorporeal perfusion support is needed to achieve ROSC, although use in HiTCA with post-ROSC hemodynamic instability might also be considered up to the time limit for aortic balloon occlusion. This modality is similar to VA-ECLS but the perfusion is limited to the aortic arch and uses smaller catheters, and therefore lower infusion rates, to accomplish perfusion support. When ROSC is achieved, the SAAP catheter balloon is deflated as soon as possible whilst observing for hemodynamic decompensation, and the catheter removed as soon it is apparent that endovascular resuscitation is no longer required. As already noted, the total SAAP balloon inflation time should be less than 30 minutes. However, every effort should be made to deflate the balloon as soon as possible. If ROSC is achieved but intrinsic perfusion and arterial blood pressure are inadequate, transition to the next SAAP modality proceeds.

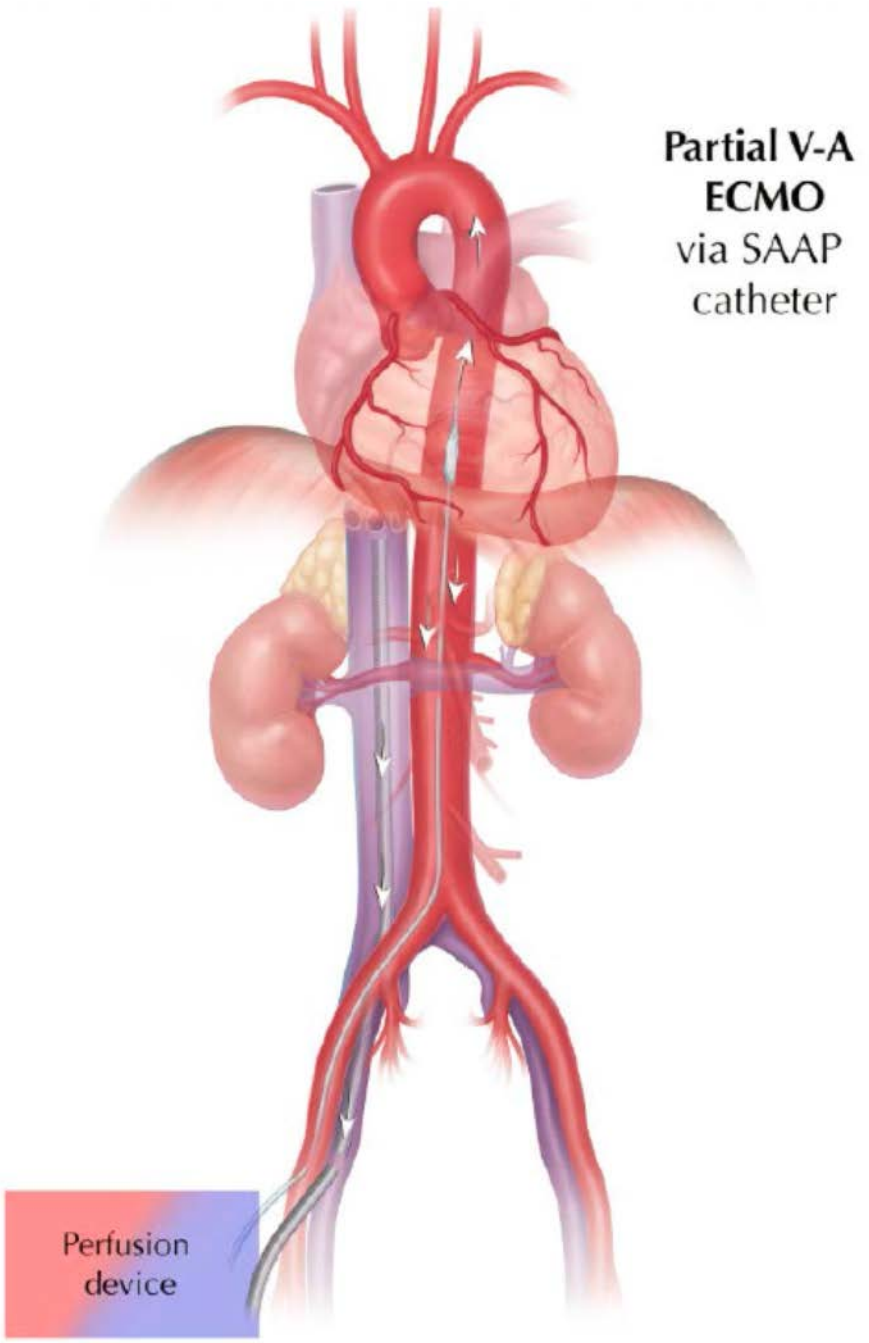
SAAP with oxygenated autologous blood



Limited whole body SAAP catheter perfusion support

The third SAAP modality is essentially the continuation of SAAP with autologous blood but with the SAAP catheter balloon deflated. Since the perfusion is not restricted to the aortic arch in this modality, it is technically no longer SAAP but simply using the SAAP catheter to provide a limited degree of whole body veno-arterial perfusion support. The maximum perfusion support in this modality is approximately 800-1000 mL/min. This SAAP modality is indicated in patients who have achieved ROSC but are not hemodynamically stable post-ROSC and may need to be transitioned to VA-ECLS for prolonged perfusion support. If the patient improves hemodynamically over the short-term (approximately 30 minutes), the SAAP modality may be withdrawn without the need for transition to VA-ECLS. However, this SAAP modality primarily serves as bridging support until larger cannulas can be placed for transition to VA-ECLS. The time period for transition to V-A ECLS will depend upon various factors. This SAAP modality may be used for longer if the patient needs to be transported to the hospital or to another location to initiate V-A ECLS. If anticoagulation has not been initiated up to this point, it should be considered again during this phase. The use of this SAAP modality to allow for cardiac catheterization and coronary intervention is theoretical currently.

Continued perfusion support after ROSC with the SAAP catheter balloon deflated can serve as a perfusion bridge until transition to V-A ECMO.


Partial V-A
ECMO
via SAAP
catheter
Perfusion
device

Transition from SAAP Catheter to VA-ECLS

Patients requiring extracorporeal perfusion support for a prolonged time period (days to weeks) will need to be transitioned to VA-ECLS. The role of SAAP ends with ROSC and early temporary post-ROSC perfusion support. The transition to V-A ECLS can either be accomplished by cannulation of the femoral artery and vein contralateral to the SAAP catheter (allowing seamless transition and uninterrupted perfusion support), or by removal of the SAAP catheter over a guidewire and upsizing the same artery to an arterial ECLS cannula (with a brief loss of perfusion support). The choice may be influenced by factors such as anatomical considerations and the circumstances under which the SAAP catheter was inserted.

SAAP Key Points:

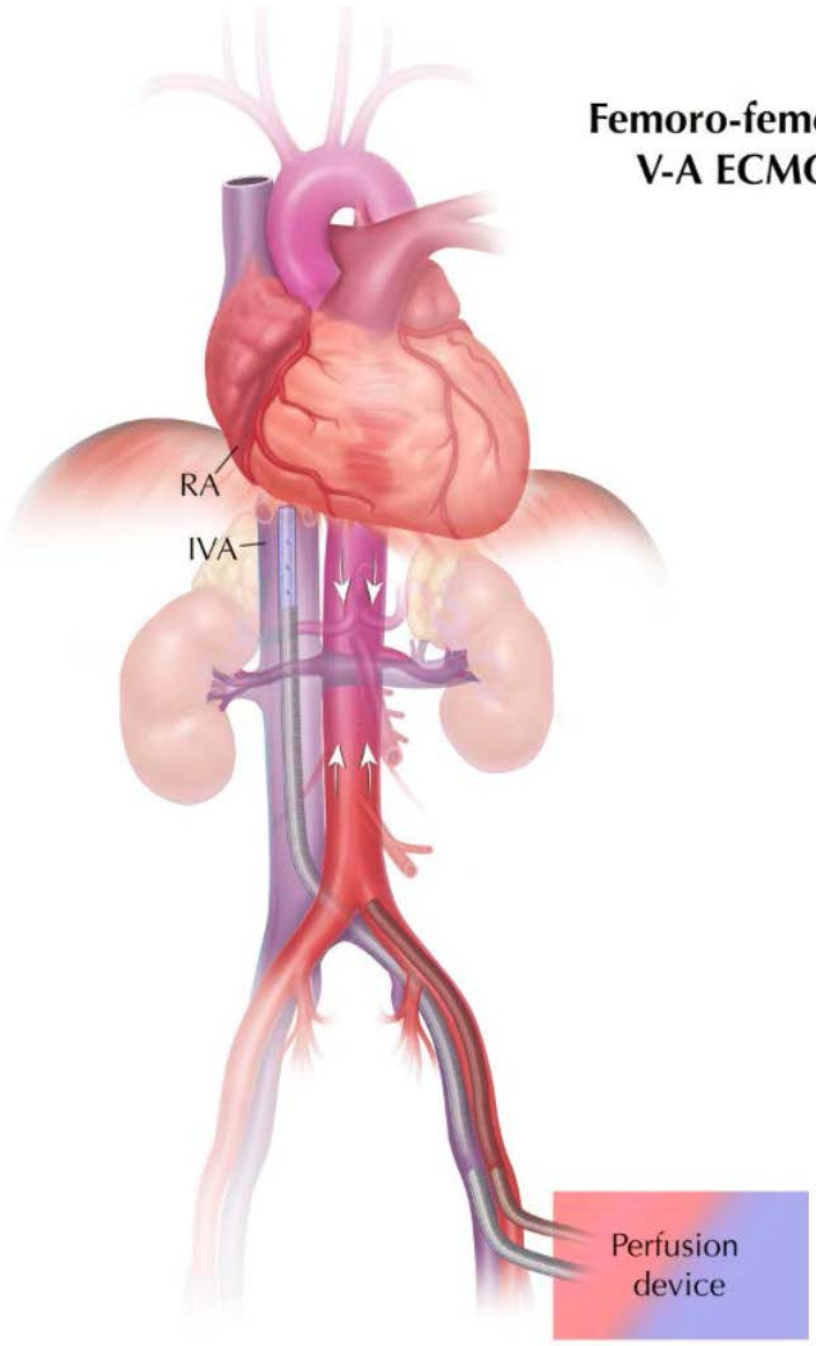
SAAP is indicated for cardiac arrest or impending cardiac arrest.

SAAP requires only femoral arterial access to begin perfusion support.

Close the aortic valve with an initial rapid bolus.

During initial SAAP with Exogenous Oxygen Carrier gain initial femoral venous access.

Transition to SAAP with autologous blood, if needed, to achieve ROSC or promote stability.

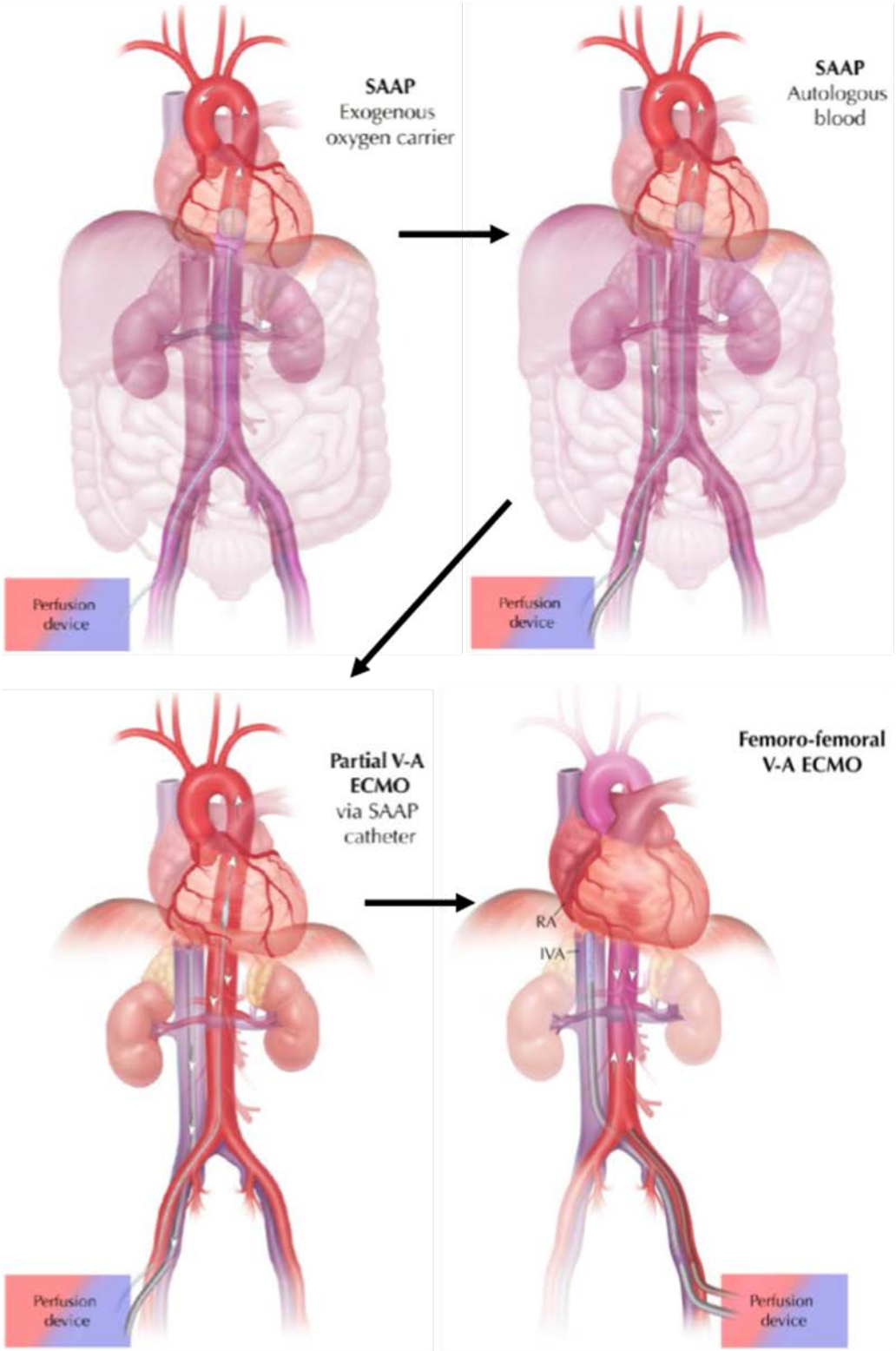

Femoro-femoral
V-A ECMO
RA
IVA
Perfusion
device

Where does SAAP fit in Endovascular Resuscitation

SAAP is an endovascular resuscitation therapy developed specifically for cardiac arrest that has features in common with both V-A ECLS and REBOA. SAAP is primarily an extracorporeal heart and brain perfusion technique to promote ROSC from cardiac arrest. However, the thoracic aortic balloon occlusion integral to SAAP therapy provides hemorrhage control caudal to the balloon consistent with Zone 1 REBOA. These shared features make SAAP applicable to both medical cardiac arrest and HiTCA, but SAAP is not the same as either V-A ECLS or REBOA. This raises the question of how SAAP should be integrated into both medical and trauma resuscitation strategies.

Hemorrhage-Induced Traumatic Cardiac Arrest

In severe hemorrhagic shock leading to impending or true cardiac arrest, SAAP is an intervention that bridges the gap between REBOA hemorrhage control and resuscitative thoracotomy with manual cardiac compression to generate myocardial perfusion. REBOA (Zone 1 or Zone 3) is an effective means of hemorrhage control that allows for intravenous volume resuscitation and transfer to the operating theater or interventional radiology suite for definitive hemorrhage control. REBOA, particularly in Zone 1, increases systemic vascular resistance and supports mean arterial pressure while intravenous fluid and blood resuscitation catch-up with hemorrhage-induced intravascular volume loss. REBOA is most effective when deployed while the heart is still beating well and there is a discernible arterial blood pressure. When patients become bradycardic and lose measurable blood pressure, this is a state of impending cardiac arrest. REBOA can be effective at this point but only if the heart continues to beat and intravenous


SAAP
Exogenous
oxygen carrier
SAAP
Autologous
blood
Perfusion
device
Perfusion
device
Partial V-A
ECMO
via SAAP
catheter
Femoro-femoral
V-A ECMO
RA
IVA
Perfusion
device
Perfusion
device

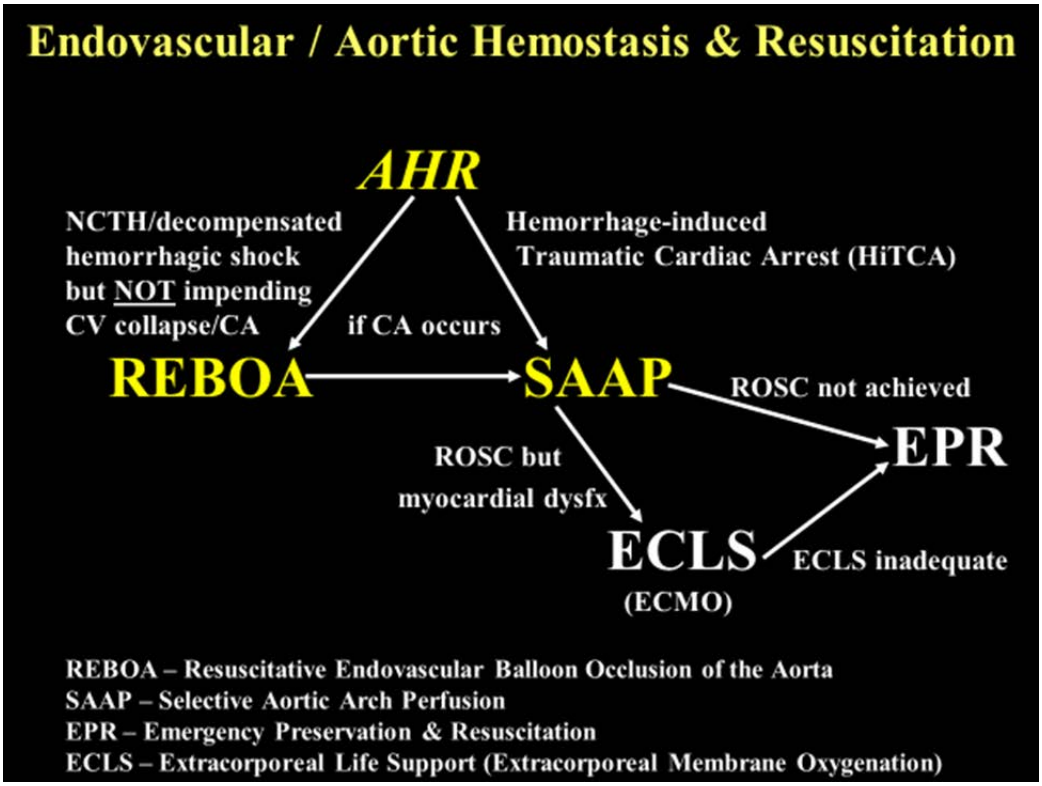
blood transfusion rapidly corrects the volume and perfusion deficit. Traditionally, this is the point at which resuscitative thoracotomy is either performed, or at least considered, before cessation of resuscitation efforts.

SAAP offers extracorporeal perfusion to aortic balloon occlusion hemorrhage control in the setting of true cardiac arrest due to hemorrhage or impending cardiac arrest with rapidly dropping heart rate and extremely low, nonviable blood pressure. The combination of thoracic aortic balloon occlusion (functional aortic cross-clamp), extracorporeal perfusion with exogenous oxygen-carrier (more effective than manual cardiac compression), and rapid intravascular volume replacement (equivalent to or better than intravenous infusion) provided for by the SAAP technique can serve to promote ROSC without the need for a thoracotomy and bridge survival until the patient can be transferred to the operating theater for definitive hemorrhage control. Therefore, in the setting of hemorrhage-induced cardiac arrest, SAAP is an intervention between REBOA and resuscitative thoracotomy that can potentially achieve ROSC and obviate the need for thoracotomy.

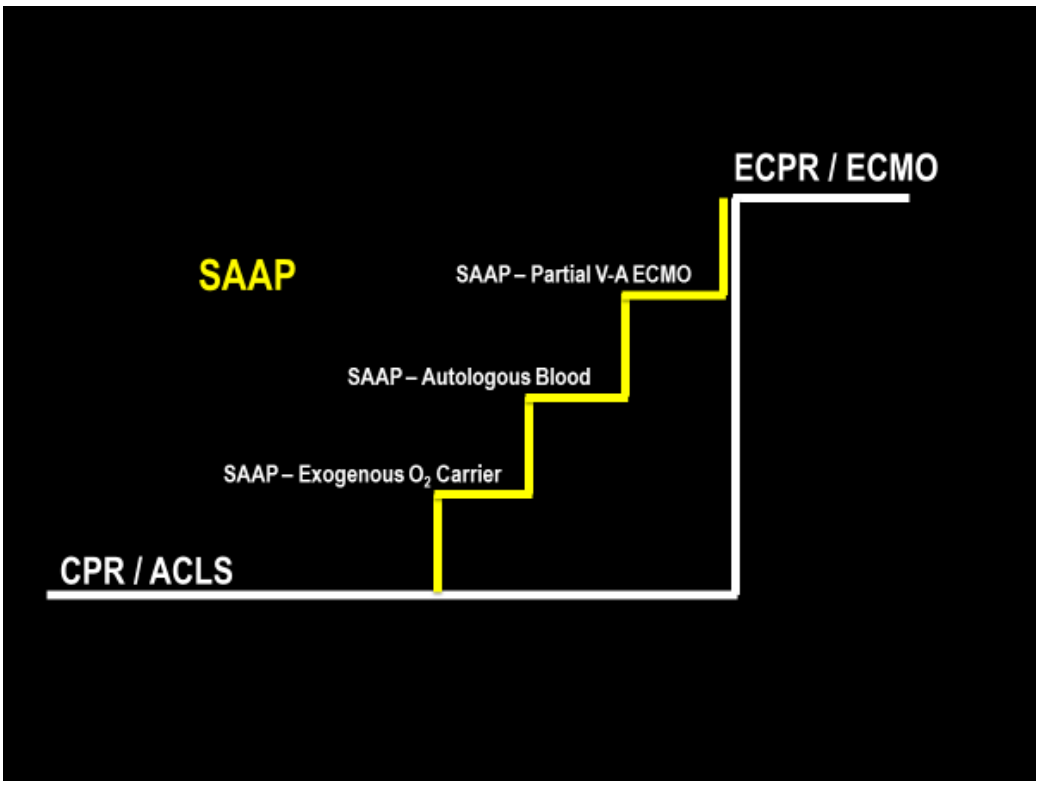
Medical Cardiac Arrest

In medical cardiac arrest, the potential role of SAAP lies between standard resuscitation therapies of the present day, the foundation of which is closed-chest CPR, and the implementation of VA-ECLS during cardiac arrest or ECPR. A proportion of medical cardiac arrest victims can be resuscitated with closed-chest CPR and defibrillation, if bystander CPR is initiated without delay and an automated defibrillator is nearby and used appropriately. However, these two conditions are infrequently met. Delays in CPR and defibrillation lead to decreased effectiveness of CPR and degraded electrical energy respectively that result in preventable

SAAP in TRAUMA



SAAP in MEDICAL CARDIAC ARREST



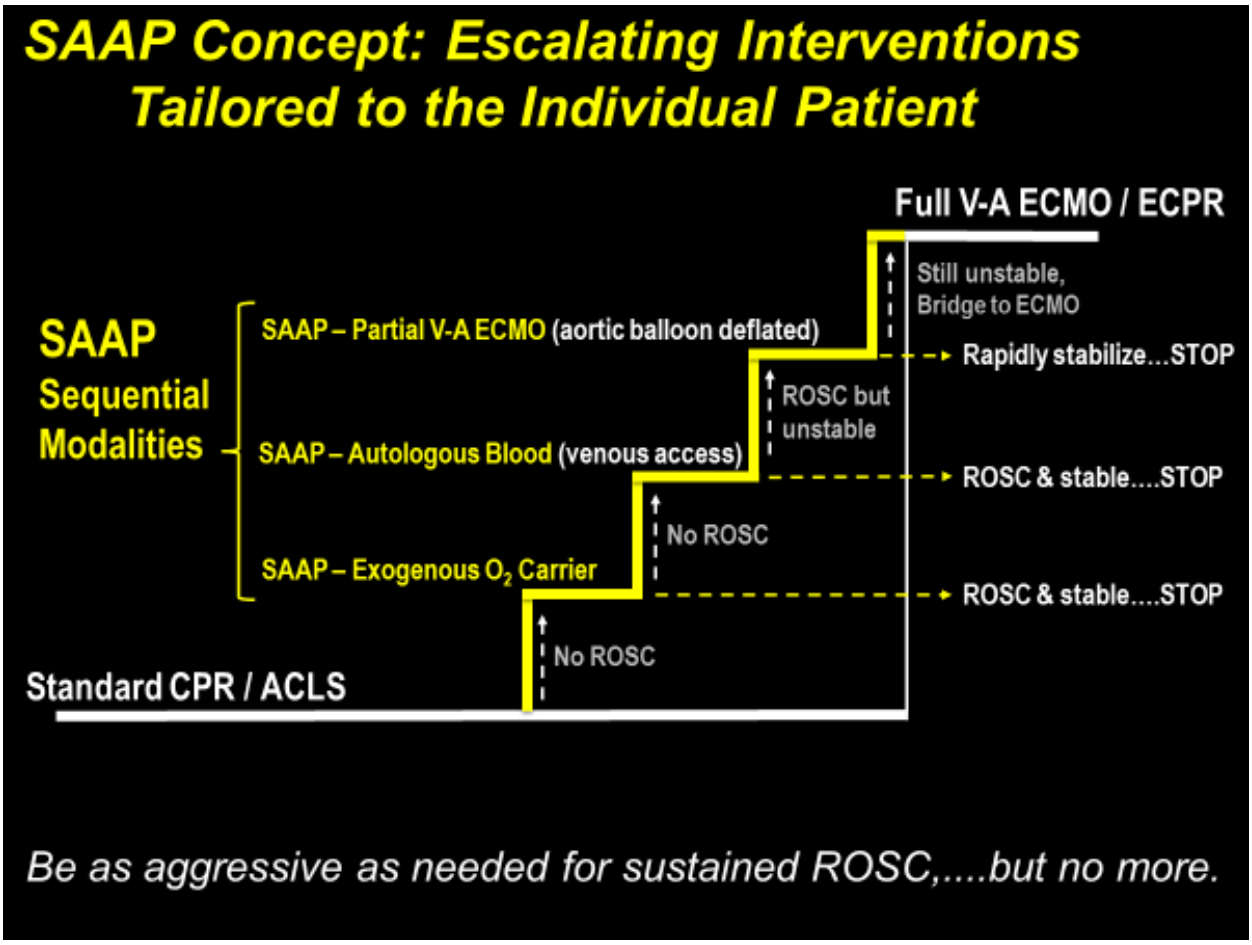
deaths just as uncontrolled hemorrhage with severe hypoperfusion does in trauma. V-A ECLS/ECPR provides extracorporeal perfusion that can effectively reverse the ischemic debt that occurs during cardiac arrest and lead to ROSC and long-term survival. Clinical reports are very promising with remarkably high survival with good neurological recovery in the patients that meet criteria for ECPR.

An important aspect of VA-ECLS is that once a patient has been cannulated during cardiac arrest for ECPR and had achieved ROSC, the patient remains on V-A ECLS. The duration of V-A ECLS support after ROSC is typically several days. In general, V-A ECLS is not an intervention that can be quickly discontinued. It usually requires surgical decannulation and vascular repair in an operating theater. Although some resuscitated patients need ongoing perfusion support post-ROSC, some do not. This issue is faced when trying to determine the appropriate criteria for committing the resources required to perform V-A ECLS/ECPR. In some systems, standard therapy is continued for 20 minutes before the patient is considered for V-A ECLS/ECPR to avoid overutilization. There is a tension between waiting too long to initiate V-A ECLS/ECPR and overutilization without any clear parameters to distinguish the appropriate choice.

Temporary heart and brain perfusion during cardiac arrest may be adequate to achieve ROSC and promote long-term survival without the need for prolonged ECLS support. This is the niche that SAAP is designed to fill. The sequence of SAAP interventions previously described could be initiated early in resuscitation after initial CPR and defibrillation have failed without committing to prolonged ECLS support. If ROSC is achieved and the patient is hemodynamically stable post-ROSC, SAAP can be withdrawn rapidly. However, if the patient's condition shows a need for ongoing ECLS support, SAAP interventions can be used to provide bridging

support until cannulation for V-A ECLS can be accomplished. Thus, SAAP in medical cardiac arrest may promote ROSC and favorable neurological recovery without committing patients to extended ECLS support post-ROSC. However, if ongoing ECLS support is needed, SAAP serves as a bridge to ECMO. Therefore, in the setting of medical cardiac arrest, SAAP is an intervention between closed-chest CPR and V-A ECLS that can potentially achieve ROSC and prevent unnecessary prolonged ECLS support.

SUMMARY of SAAP CONCEPT



END

SAAP in Hemorrhage-Induced Traumatic Cardiac Arrest

Laboratory studies in porcine models for severe HiTCA have demonstrated the efficacy of SAAP with both blood products and HBOC-201, and also tested the SAAP modalities as an escalating paradigm. The first experiments defined the translation of SAAP in medical cardiac arrest to HiTCA, and the use of shed autologous blood was found to be efficacious. In these experiments, the shed blood was heparinized to prevent clot formation before reinfusion. Thus, the issue of citrate anticoagulant-related ionized hypocalcemia was not addressed in these experiments. Nonetheless, these first experiments in a HiTCA model demonstrated that oxygenated whole blood could effectively achieve ROSC.

In recognition of the potential for limited blood product availability prehospital and the favorable characteristics of a room temperature stable HBOC with a long shelf-life, SAAP was subsequently examined using HBOC-201 compared to lactated Ringer's solution in a model of liver trauma resulting in a brady-asystolic HiTCA. This study showed that SAAP with oxygenated HBOC-201 without CPR or intra-aortic epinephrine resulted in consistent ROSC after about two minutes of therapy. Two animals receiving SAAP with lactated Ringer's solution had very brief ROSC aided by the addition of intra-aortic epinephrine. This study further emphasized the need for a perfusate with adequate oxygen-carrying capacity.

The lack of regulatory approval of any non-blood oxygen carrier over time led to a renewed interest in blood products serving as the SAAP oxygen-carrying perfusate. Although the early experiments using SAAP with oxygenated whole blood achieved ROSC, the correction of ionized calcium in citrate anticoagulated blood had not been demonstrated. It was recognized that citrate anticoagulated blood has a nondetectable ionized calcium level and perfusion of the heart with

such blood without correction of the ionized calcium would result in refractory ventricular fibrillation. To address this issue, a series of experiments was performed utilizing stored, citrate anticoagulated whole blood and packed red cells as the SAAP perfusate combined with calcium infusion to yield ionized calcium levels in the normal range. The combination prevented hypocalcemia-induced ventricular fibrillation and demonstrated the ability of achieve ROSC with the concomitant administration of calcium with citrate anticoagulated blood products. **FIGURE 6** These experiments provided data for the methods and quantification of concomitant calcium administration for SAAP with both whole blood and packed red blood cells.

In order to characterize the level of hemorrhagic injury that SAAP could effectively resuscitate and to make comparison with current and evolving resuscitation strategies, SAAP with fresh whole blood (FWB) was evaluated against SAAP with oxygenated lactated Ringer's solution, Zone 1 REBOA with intravenous FWB, and CPR with intravenous FWB. The porcine model was a hybrid of liver injury and controlled arterial hemorrhage that resulted in a brady-asystolic arrest; 30% of the animals were in electrocardiographic asystole (a very severe HiTCA). SAAP with oxygenated FWB resulted in significantly higher rates of ROSC and significantly higher 60-minute survival than the other three interventions. **FIGURE 7** In addition, SAAP with FWB was demonstrated to be capable of resuscitating hemorrhage-induced cardiac asystole in large swine.

More recent experiments have examined the use of sequential, escalating endovascular intervention in HiTCA: Zone 1 REBOA with intravenous FWB (REBOA), followed by SAAP with exogenous FWB (SAAP), followed by a SAAP circuit with autologous blood (SAAP-circuit) as required. This paradigm resulted in two animals

(unexpectedly) achieving ROSC in the REBOA group, two animals achieving ROSC in the SAAP group, and four animals achieving ROSC in the SAAP-circuit group – all survived the 60-minute simulated prehospital period. This set of experiments demonstrated two important concepts in HiTCA resuscitation: (1) that even in laboratory conditions it is challenging to predict whether REBOA with intravenous blood will result in a ROSC, and (2) that a paradigm of escalating intervention improves the risk:benefit of endovascular intervention by only exposing the subject to the risk of the intervention(s) required to achieve a ROSC, whilst providing vital brain perfusion after a prolonged arrest.

Most recently, renewed interest in HBOCs for austere environments, such as the battlefield, led to further investigation of SAAP with oxygenated HBOC for resuscitation of HiTCA. In a laboratory model of liver injury and HiTCA, SAAP using oxygenated fresh whole blood was compared with SAAP using oxygenated HBOC-201 to evaluate ROSC and five hours post-ROSC survival and physiological status. This study found that ROSC rates were not statistically different and physiological recovery was similar for the two groups over the five-hour post-ROSC observation period; for example, the similar spectrum of five-hour lactate levels as an indicator of hemodynamic stability, perfusion status and metabolic recovery. **FIGURE 8**

The use of SAAP in thoracic trauma has not been adequately studied to date. One small series of experiments evaluated SAAP in a porcine model of HiTCA with associated large pericardial tamponade resulting in electrical and mechanical cardiac asystole. **FIGURE 9** SAAP restored an organized ECG rhythm and cardiac contractility with the 200 mL tamponade was still in place. The aortic arterial pressure was low with the tamponade, but sequential removal of 50 mL from the

pericardial sac resulted in corresponding increases in central aortic pressure. **FIGURE 10**

Advantages and Limitations of SAAP

SAAP in Hemorrhage-Induced Traumatic Cardiac Arrest

In HiTCA, SAAP provides resuscitative perfusion to achieve ROSC, rapid intravascular volume restoration, and aortic balloon occlusion distal hemorrhage control. Thus, SAAP accomplishes three of the aims of resuscitative thoracotomy using a single balloon catheter, and in doing so reduces the risk to providers, the additional physiological insult in the patient of a major surgical procedure, and can be employed earlier in the hemorrhage spectrum (impending versus true cardiac arrest) with a greater expectation of survival. In addition, intermittent aortic pressure measurement can be quickly performed to assess for ROSC and determination if SAAP needs to be continued or stopped.

If stored (allogeneic) blood is used as the exogenous perfusate for SAAP, it must be accurately matched with calcium to assure the perfusate has a normal ionized calcium at aortic infusion. The perfusion support provided by SAAP in temporary and intended to achieve a ROSC. If a patient resuscitated by SAAP requires ongoing post-ROSC perfusion support for many hours or days, the patient needs to be transitioned to ECLS - SAAP cannot provide prolonged support. However, as previously explained, the paradigm of sequential, escalating SAAP modalities potentially clarifies the risk:benefit decision-making of endovascular resuscitation.

Where does SAAP fit in Endovascular Resuscitation

SAAP is an endovascular resuscitation therapy developed specifically for cardiac arrest that has features in common with both V-A ECLS and REBOA. SAAP is primarily an extracorporeal heart and brain perfusion technique to promote ROSC from cardiac arrest. However, the thoracic aortic balloon occlusion integral to SAAP therapy provides hemorrhage control caudal to the balloon consistent with Zone 1 REBOA. These shared features make SAAP applicable to both medical cardiac arrest and HiTCA, but SAAP is not the same as either V-A ECLS or REBOA. This raises the question of how SAAP should be integrated into both medical and trauma resuscitation strategies.

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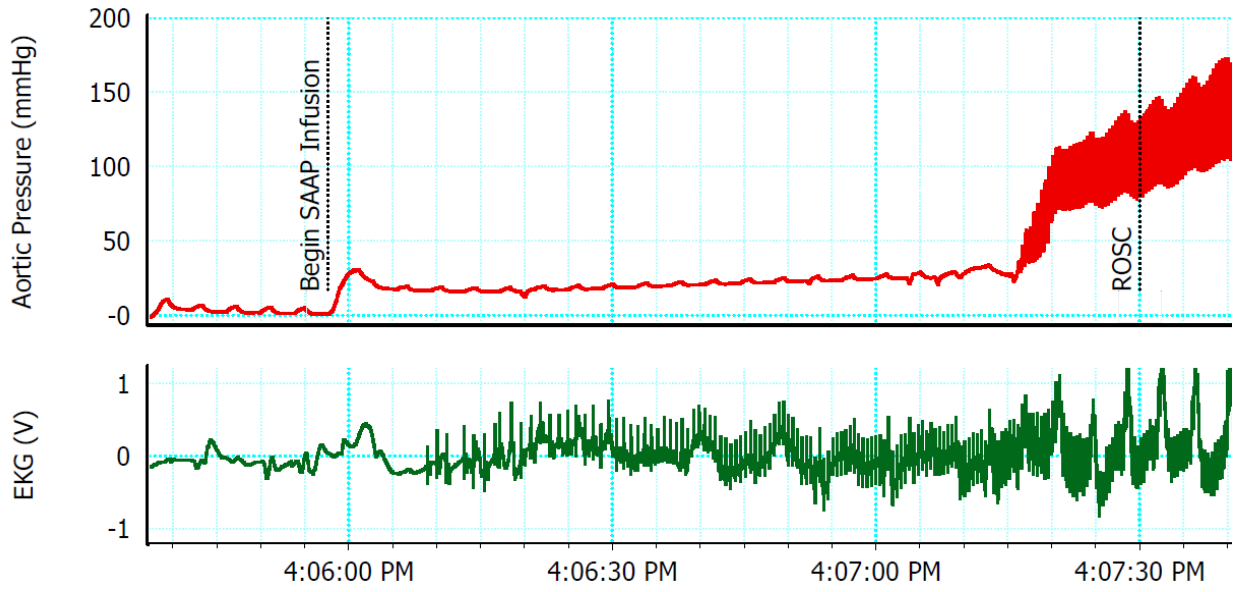
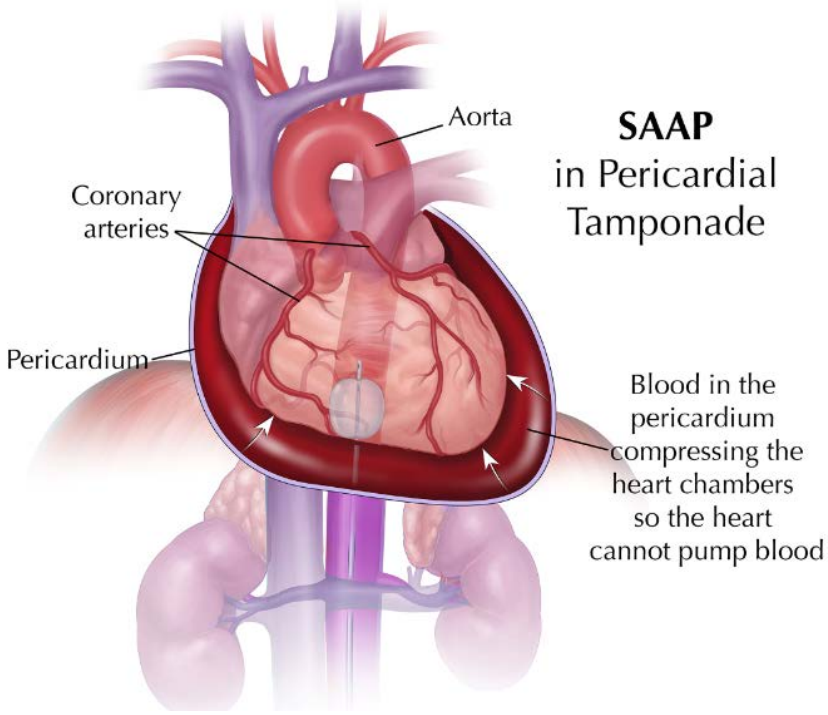
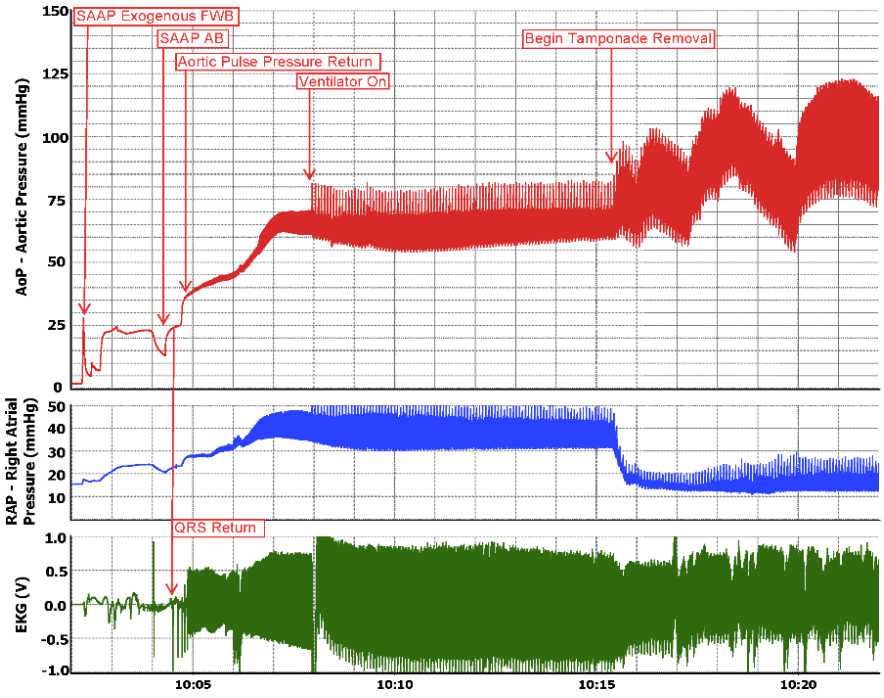
SAAP offers extracorporeal perfusion to aortic balloon occlusion hemorrhage control in the setting of true cardiac arrest due to hemorrhage or impending cardiac arrest with rapidly dropping heart rate and extremely low, nonviable blood pressure. The combination of thoracic aortic balloon occlusion (functional aortic cross-clamp), extracorporeal perfusion with exogenous oxygen-carrier (more effective than manual cardiac compression), and rapid intravascular volume replacement (equivalent to or better than intravenous infusion) provided for by the SAAP technique can serve to promote ROSC without the need for a thoracotomy and bridge survival until the patient can be transferred to the operating theater for definitive hemorrhage control. Therefore, in the setting of hemorrhage-induced cardiac arrest, SAAP is an intervention between REBOA and resuscitative thoracotomy that can potentially achieve ROSC and obviate the need for thoracotomy.




Aorta
Coronary arteries
Pericardium
SAAP
in Pericardial Tamponade
Blood in the pericardium compressing the heart chambers so the heart cannot pump blood


SAAP Exogenous FWB
SAAP AB
Aortic Pulse Pressure Return
Ventilator On
Begin Tamponade Removal
AoP - Aortic Pressure (mmHg)
150
125
100
75
50
25
0
RAP - Right Atrial Pressure (mmHg)
50
40
30
20
10
QRS Return
EKG (V)
1.0
0.5
0.0
-0.5
-1.0
10:05
10:10
10:15
10:20

SAAP in Medical Cardiac Arrest – Sudden Cardiac Death

SAAP in Ventricular Fibrillation Cardiac Arrest

The first SAAP experiments investigated infusion rates to gain insight into the effective flow rates and limits to volume loading. Fluoroscopic studies identified the need for the initial rapid bolus to pressurize the aorta and close the aortic valve. Myocardial blood flow during SAAP was measured by colored microspheres and was demonstrated to be greater than baseline myocardial blood flow when the heart was beating normally prior to induction of cardiac arrest, in the range of 120-150% of baseline on average. The reason for this supra-normal blood flow is that the heart in cardiac arrest can be perfused continuously compared to the normal state of the beating heart which only receives blood flow during the diastolic phase of the cardiac cycle. Continuous SAAP infusion without CPR chest compressions and pulsed SAAP infusion timed with the diastolic phase of CPR chest compressions did not show any significant difference in myocardial blood flow during cardiac arrest by colored microsphere measurements. Given the importance of avoiding aortic valve incompetence, subsequent research studies have performed SAAP without CPR chest compressions to avoid potential inadvertent compromise of aortic valve closure.

Controlled laboratory comparisons of SAAP using perfluorocarbon emulsions as the oxygen carrier showed improved ROSC compared to control using standard noninvasive resuscitation therapy. The time limit for infusion of an exogenous oxygen carrier in medical cardiac arrest with euvolemia led to the second SAAP modality of using autologous blood as the oxygenated perfusate. This required the addition of a femoral venous blood withdrawal catheter advancing the concept that

femoral venous access would be obtained during the initial SAAP-exogenous oxygen carrier therapy. Thus, SAAP with autologous blood does not prolong the time to initiate SAAP but adds a means of sustained SAAP without further volume loading. SAAP with autologous blood is similarly effective at achieving ROSC from ventricular fibrillation cardiac arrest. **FIGURE 5** Intra-aortic epinephrine administration has been studied alone and as an adjunct to SAAP during cardiac arrest. The use of small doses of intra-aortic epinephrine during cardiac arrest has been shown to be useful for promoting ROSC. More recently, a comparison of standard noninvasive resuscitation and SAAP with oxygenated HBOC-201 in a ventricular fibrillation model showed improved ROSC with SAAP-HBOC.

Advantages and Limitations of SAAP

Compared to standard resuscitation with closed-chest CPR and other endovascular resuscitation techniques, SAAP has both advantages and limitations that vary depending upon the cause of cardiac arrest.

The principal advantage of SAAP over closed-chest CPR is the scale of myocardial perfusion that can be generated. Whereas closed-chest CPR at best generates a fraction of normal myocardial blood flow, SAAP generates myocardial perfusion that is even greater than normal physiological blood flow generated by a healthy beating heart. Closed-chest CPR aims to increase aortic pressure and generate a CPP gradient sufficient to drive myocardial blood flow (as well as providing cerebral perfusion). SAAP is an extracorporeal perfusion therapy that provides a known, predetermined level of perfusion. The aortic pressure generated is secondary to the SAAP infusion and can be adjusted using intra-aortic epinephrine.

Compared to VA-ECLS, SAAP can be initiated more quickly by a single provider because it only requires arterial access to begin perfusion support. V-A ECLS requires both arterial and venous access with larger cannulas and a closed perfusion circuit to initiate perfusion. The SAAP catheter has a smaller outer diameter than an arterial ECLS cannula and does not require serial dilation steps for insertion. The larger ECLS cannulas generally require removal in the operating theater with surgical vascular repair. The smaller SAAP catheter can be removed quickly and should typically not require surgical intervention. Because SAAP can be removed quickly and does not commit the patient to several days of extracorporeal perfusion support, it could be initiated earlier in resuscitation with fewer concerns for excessive intervention, and iatrogenic complications.

The major limitation of SAAP with an exogenous oxygen-carrier is that it is a volume-loading procedure and is time-limited, particularly in euvolemic or volume-overloaded patients – most applicable in medical cardiac arrest. Potential adverse effects of volume overload due to SAAP are most relevant in medical cardiac arrest and least likely in severe hemorrhage.

Where does SAAP fit in Endovascular Resuscitation

SAAP is an endovascular resuscitation therapy developed specifically for cardiac arrest that has features in common with both V-A ECLS and REBOA. SAAP is primarily an extracorporeal heart and brain perfusion technique to promote ROSC from cardiac arrest. However, the thoracic aortic balloon occlusion integral to SAAP therapy provides hemorrhage control caudal to the balloon consistent with Zone 1 REBOA. These shared features make SAAP applicable to both medical cardiac arrest and HiTCA, but SAAP is not the same as either V-A ECLS or REBOA. This raises the

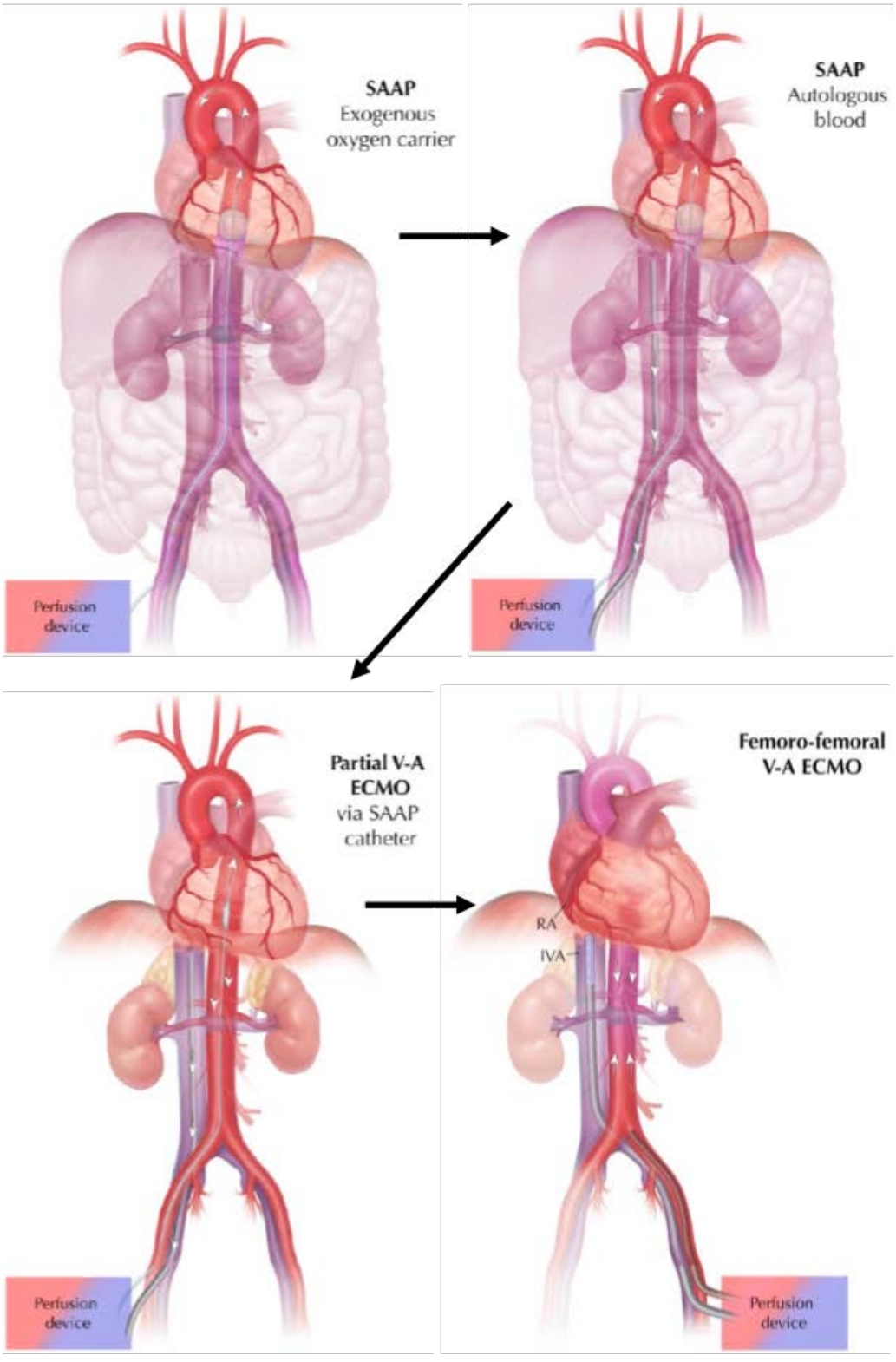
question of how SAAP should be integrated into both medical and trauma resuscitation strategies.

In medical cardiac arrest, the potential role of SAAP lies between standard resuscitation therapies of the present day, the foundation of which is closed-chest CPR, and the implementation of VA-ECLS during cardiac arrest or ECPR. A proportion of medical cardiac arrest victims can be resuscitated with closed-chest CPR and defibrillation, if bystander CPR is initiated without delay and an automated defibrillator is nearby and used appropriately. However, these two conditions are infrequently met. Delays in CPR and defibrillation lead to decreased effectiveness of CPR and degraded electrical energy respectively that result in preventable deaths just as uncontrolled hemorrhage with severe hypoperfusion does in trauma. V-A ECLS/ECPR provides extracorporeal perfusion that can effectively reverse the ischemic debt that occurs during cardiac arrest and lead to ROSC and long-term survival. Clinical reports are very promising with remarkably high survival with good neurological recovery in the patients that meet criteria for ECPR.

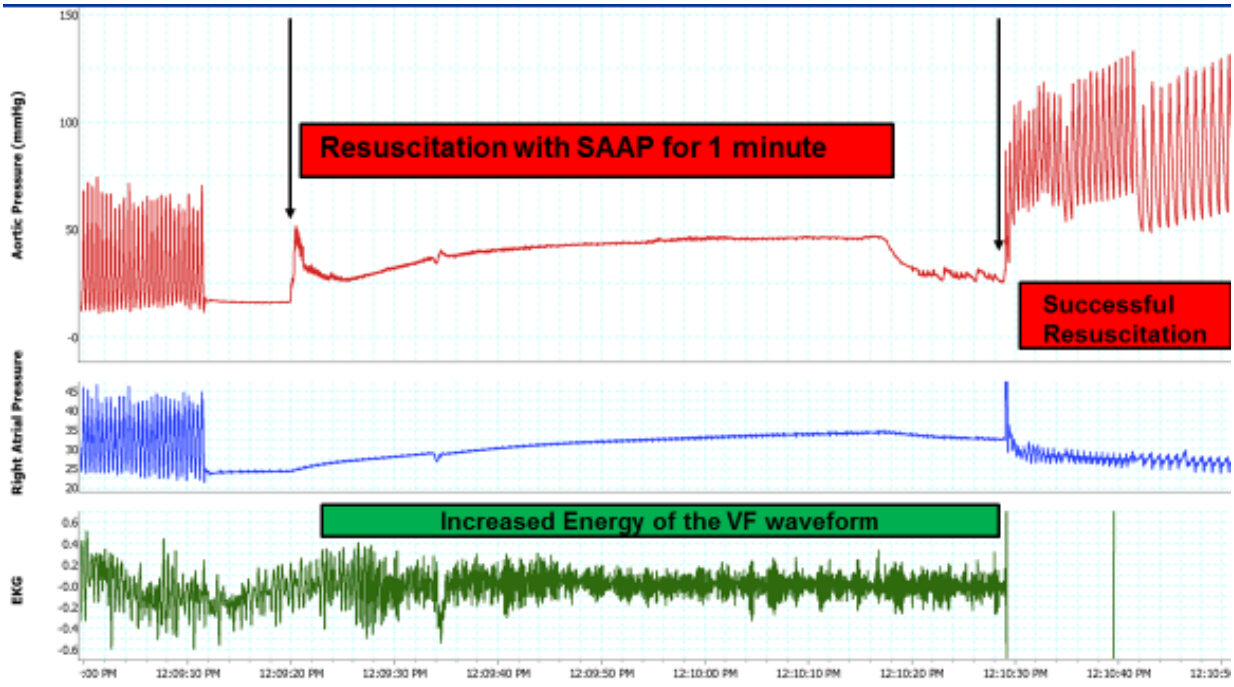
An important aspect of VA-ECLS is that once a patient has been cannulated during cardiac arrest for ECPR and had achieved ROSC, the patient remains on V-A ECLS. The duration of V-A ECLS support after ROSC is typically several days. In general, V-A ECLS is not an intervention that can be quickly discontinued. It usually requires surgical decannulation and vascular repair in an operating theater. Although some resuscitated patients need ongoing perfusion support post-ROSC, some do not. This issue is faced when trying to determine the appropriate criteria for committing the resources required to perform V-A ECLS/ECPR. In some systems, standard therapy is continued for 20 minutes before the patient is considered for V-A ECLS/ECPR in an effort to avoid overutilization. There is a tension between

waiting too long to initiate V-A ECLS/ECPR and overutilization without any clear parameters to distinguish the appropriate choice.

Temporary heart and brain perfusion during cardiac arrest may be adequate to achieve ROSC and promote long-term survival without the need for prolonged ECLS support. This is the niche that SAAP is designed to fill. The sequence of SAAP interventions previously described could be initiated early in resuscitation after initial CPR and defibrillation have failed without committing to prolonged ECLS support. If ROSC is achieved and the patient is hemodynamically stable post-ROSC, SAAP can be withdrawn rapidly. However, if the patient's condition shows a need for ongoing ECLS support, SAAP interventions can be used to provide bridging support until cannulation for V-A ECLS can be accomplished. Thus, SAAP in medical cardiac arrest may promote ROSC and favorable neurological recovery without committing patients to extended ECLS support post-ROSC. However, if ongoing ECLS support is needed, SAAP serves as a bridge to ECMO. Therefore, in the setting of medical cardiac arrest, SAAP is an intervention between closed-chest CPR and V-A ECLS that can potentially achieve ROSC and prevent unnecessary prolonged ECLS support.


SAAP
Exogenous
oxygen carrier
Perfusion
device
SAAP
Autologous
blood
Perfusion
device
Partial V-A
ECMO
via SAAP
catheter
Perfusion
device
Femoro-femoral
V-A ECMO
RA
IVA
Perfusion
device

Figure


Aortic Pressure (mmHg)
150
100
50
0
Resuscitation with SAAP for 1 minute
Successful Resuscitation
Right Atrial Pressure
Increased Energy of the VF waveform
EKG
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
12:09:10 PM
12:09:20 PM
12:09:30 PM
12:09:40 PM
12:09:50 PM
12:10:00 PM
12:10:10 PM
12:10:20 PM
12:10:30 PM
12:10:40 PM

APPENDIX

SAAP Handout – Initial Resuscitation Steps

SAAP Handout – Additional Resuscitation Steps

Selective Aortic Arch Perfusion:

Initial Resuscitation Steps

1 – Inflate SAAP Catheter Balloon, 10-15 mL of fluid

2 – Make Sure the Perfusion System is Ready to Go

3 – Draw up 50 mL of Perfusate in the Bolus Syringe

4 – Rapid 50 mL Bolus / 2-3 sec to Close the Aortic Valve

5 – Switch Without Delay to Running Perfusion System

6 – Observe ECG for Rhythm Change

7 – Monitor Perfusate Volume & Manage as Needed

Selective Aortic Arch Perfusion:

Additional Resuscitation Steps

– Consider intra-aortic low dose diluted epinephrine
(100-250 mcg increments, q 60 sec, guided by AoP response)

– Evaluate pulses or cardiac US to assess for ROSC

– Stop SAAP and Check for AoP pulsations, if indicated

– Add Perfusate to the Perfusion System, as needed

– If SAAP Stopped & No AoP / ROSC: Resume with Bolus

– If SAAP Stopped & ROSC: Monitor AoP for decline

– Consider Balloon Deflation, Complete or Partial, ASAP