

Retrograde Inferior Vena Caval Perfusion for Total Aortic Arch Replacement Surgery (RIVP-TARS): A Multicenter, Randomized, Controlled, Double-Blind Trial

Jing Lin

Sichuan University West China Hospital

Zhaoxia Tan

Sichuan University West China Hospital

Xiaolin Hu

First Affiliated Hospital of University of South China

Hao Yao

Cardiovascular Center of the Second Affiliated Hospital Nanjing Medical University

Dafa Zhang

First Affiliated Hospital Wannan Medical University

Yuan Zhao

The Second Xiangya Hospital

Jiyue Xiong

Sichuan University West China Hospital

Bo Dou

First Affiliated Hospital of University of South China

Xueshuang Zhu

First Affiliated Hospital Wannan Medical University

Zhong Wu

Sichuan University West China Hospital

Yingqiang Guo

West China Hospital Sichuan University

Deying Kang

Sichuan University West China Hospital

Lei Du (✉ dulei@scu.edu.cn)

Sichuan University West China Hospital

Method Article

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Abstract

Background: During total aortic arch replacement surgery (TARS) for patients with acute type A aortic dissection, organs in the lower body such as the viscera and spinal cord are at risk of ischemia even when antegrade cerebral perfusion (ACP) is performed. Combining ACP with retrograde inferior vena caval perfusion (RIVP) during TARS may improve outcomes by providing the lower body with oxygenated blood.

Methods: This is a multi-center, randomized, controlled trial of 500 patients scheduled for TARS. Patients were randomly allocated to a moderate hypothermia circulatory arrest (MHCA) group, who received selective ACP with moderate hypothermia during TARS; or to an RIVP group, who received the combination of RIVP and selective ACP under moderate hypothermia during TARS. The primary outcome was a composite of early mortality and major complications, including paraplegia, postoperative renal failure, severe liver dysfunction, postoperative prolonged intubation (>48 h), and gastrointestinal complications.

Discussion: This study aims to assess whether RIVP combined with selective ACP leads to superior outcomes than selective ACP alone for patients undergoing TARS under moderate hypothermia. This study seeks to provide high-quality evidence for RIVP to be used in patients with acute type A aortic dissection undergoing TARS.

Background

Acute type A aortic dissection (AAAD) is a life-threatening condition involving tearing of the intimal layer in the ascending aorta, greater curve of the aortic arch, and proximal descending thoracic aorta. AAAD is one of the most serious cardiovascular events, with mortality rates of 50% within the first 48 hours and 75% within 2 weeks of the onset of symptoms[[endnoteRef:1](#)],[[endnoteRef:2](#)],[[endnoteRef:3](#)]. It requires immediate total aortic arch replacement surgery (TARS), in which both the ascending aorta and aortic arch are replaced with artificial vascular grafts. If necessary, a transaortic stent elephant trunk may also be implanted[[endnoteRef:4](#)]. [1: Isselbacher EM. Epidemiology of thoracic aortic aneurysms, aortic dissection, intramural hematoma, and penetrating atherosclerotic ulcers. In: Baliga RR, Nienaber CA, Isselbacher EM, Eagle KA, editors. Aortic dissection and related syndromes. New York: Springer Science; 2007. p. 3e15.] [2: Tsai TT, Trimarchi S, Nienaber CA. Acute aortic dissection: Perspectives from the International registry of acute aortic dissection (IRAD). *Eur J Vasc Endovasc Surg* 2009; 37:149-59.] [3: Moon MR. Approach to the treatment of aortic dissection. *SurgClin North Am* 2009; 89:869e93.] [4: Ma WG, Zheng J, Dong SB, Lu W, Sun K, Qi RD, Liu YM, Zhu JM, Chang Q, Sun LZ. Sun's procedure of total arch replacement using a tetrafurcated graft with stented elephant trunk implantation: analysis of early outcome in 398 patients with acute type A aortic dissection. *Ann Cardiothorac Surg*. 2013; 2:621–8.]

Because opening distal anastomosis is required during reconstruction of the aortic arch, patients may undergo a prolonged period of circulatory arrest in order to provide clinicians a clear operating field. To

minimize potential ischemic injury to organs, patients are placed under deep hypothermic circulatory arrest (DHCA), first reported by Griep and colleagues in 1975[[endnoteRef:5](#)]. DHCA is considered safe for periods of only 20-30 min at 14-20 °C[[endnoteRef:6](#)], but it is associated with high rates of mortality (13-40%)[[endnoteRef:7](#)],[[endnoteRef:8](#)], stroke (7-30%)[[endnoteRef:9](#)], and postoperative acute kidney injury (40-50%)[[endnoteRef:10](#)],[[endnoteRef:11](#)]. The risk of such events increases with DHCA duration. Furthermore, the low body temperature during DHCA can activate platelets, and the extended cardiopulmonary bypass (CPB) time for cooling and rewarming necessitates greater use of blood products than other cardiac surgeries[[endnoteRef:12](#)],[[endnoteRef:13](#)]. This had led clinicians to develop adjunct techniques that, when combined with DHCA, can improve patient outcomes; these techniques include retrograde cerebral perfusion (RCP) and selective antegrade cerebral perfusion (ACP) under mild-to-moderate hypothermic circulatory arrest. [5: Griep RB, Stinson EB, Hollingsworth JF, Buehler D. Prosthetic replacement of the aortic arch. *J Thorac Cardiovasc Surg.* 1975; 70:1051–63.] [6: Yan TD, Bannon PG, Bavaria J, Coselli JS, Elefteriades JA, Griep RB, Hughes GC, LeMaire SA, Kazui T, Kouchoukos NT, et al. Consensus on hypothermia in aortic arch surgery. *Ann Cardiothorac Surg.* 2013;2(2):163-8.] [7: Safi H.J, Miller C.C, Lee T.Y, Estrera AL. Repair of ascending and transverse aortic arch. *J Thorac Cardiovasc Surg.* 2011;142(3): 630-3.] [8: Ehrlich M, Fang WC, Grabenwoger M, Cartes-Zumelzu F, Wolner E, Havel M. Perioperative risk factors for mortality in patients with acute type a aortic dissection. *Circulation.* 1998;98(19) Suppl.: II294-8.] [9: Bavaria JE, Woo YJ, Hall RA, Wahl PM, Acker MA, Gardner TJ. Circulatory management with retrograde cerebral perfusion for acute type A aortic dissection. *Circulation.* 1996, 94(9 Suppl):173-6.] [10: Augoustides JG, Floyd TF, McGarvey ML, Ochroch EA, Pochettino A, Fulford S, Gambone AJ, Weiner J, Raman S, Savino JS. Major clinical outcomes in adults undergoing thoracic aortic surgery requiring deep hypothermic circulatory arrest: quantification of organ-based perioperative outcome and detection of opportunities for perioperative intervention. *J Cardiothorac Vasc Anesth.* 2005;19: 446–52.] [11: Arnaoutakis GJ, Bihorac A, Martin TD, Hess PJ Jr, Klodell CT, Ejaz AA, Garvan C, Tribble CG, Beaver TM. RIFLE criteria for acute kidney injury in aortic arch surgery. *J Thorac Cardiovasc Surg.* 2007; 134: 1554–60.] [12: Poucke SV, Stevens K, Marcus AE, Suzuki H, Madoiwa S, Mimuro J, Kario K, Sakata Y. Hypothermia: effects on platelet function and hemostasis. *Thrombosis Journal.* 2014; 12(1):1-5.] [13: Ziganshin BA, Elefteriades JA. Deep hypothermic circulatory arrest. *Ann Cardiothorac Surg.* 2013;2(3):303-15.]

RCP involves retrograde perfusion of cold oxygenated blood into the superior vena cava, which maintains the cerebral oxygen supply and is thought to flush out atherosclerotic debris and air generated during the repair[[endnoteRef:14](#)],[[endnoteRef:15](#)]. However, studies have suggested that combining RCP and DHCA does not reduce risk of stroke and may actually increase the risk of temporary neurologic dysfunction[[endnoteRef:16](#)]. Furthermore, RCP demands a high volume of blood products[[endnoteRef:17](#)]. [14: Hagl C, Ergin MA, Galla JD, Lansman SL, McCullough JN, Spielvogel D, Sfeir P, Bodian CA, Griep RB. Neurologic outcome after ascending aorta-aortic arch operations: effect of brain protection technique in high-risk patients. *J THORAC CARDIOV SU.* 2001.121(6):1107-21.] [15: Shenkman Z, Elami A, Weiss YG, Glantz L, Milgalter E, Drenger B, Burrows FA, Shir Y. Cerebral protection

using retrograde cerebral perfusion during hypothermic circulatory arrest. *Can J Anaesth.* 1997. 44(10):1096-101.] [16: Reuthebuch O, Schurr U, Hellermann J, Prêtre R, Künzli A, Lachat M, Turina MI. Advantages of subclavian artery perfusion for repair of acute type A dissection. *Eur J Cardiothorac Surg.* 2004;26:592-8.] [17: Apostolakis E, Koletsis E.N, Dedeilias P, Kokotsakis JN, Sakellaropoulos G, Psevdi A, Bolos K, Dougenis D. Antegrade versus retrograde cerebral perfusion in relation to postoperative complications following aortic arch surgery for acute aortic dissection type a. *J Card Surg.* 2008; 23(5): 480-7.]

The current preferred strategy for AAAD surgery is ACP+MHCA at 25-30 °C[[endnoteRef:18](#)], [[endnoteRef:19](#)]. ACP is performed by the perfusion of oxygenated blood *via* the subclavian artery, innominate artery, or the right axillary artery during hypothermic circulatory arrest (HCA). Studies show that ACP+MHCA can significantly improve clinical outcomes, leading to lower rates of mortality and neurological deficit than RCP+DHCA[[endnoteRef:20](#)],[[endnoteRef:21](#)]. Nevertheless, ACP+MHCA is associated with overall 30-day mortality rates of 5.3-19%[[endnoteRef:22](#)],[[endnoteRef:23](#)] and stroke rates of 6.7-10%.[[endnoteRef:24](#)],[[endnoteRef:25](#)] The incidence of acute kidney injury in ACP+MHCA ranges from 19 to 54%.[[endnoteRef:26](#)],[[endnoteRef:27](#)] with 5-9% of these patients requiring renal replacement therapy, which is itself associated with an elevated short-term mortality rate of 30-75%.[26](#),[[endnoteRef:28](#)] [18: Leshnower BG, Myung RJ, Kilgo PD, Vassiliades TA, Vega JD, Thourani VH, Puskas JD, Guyton RA, Chen EP. Moderate hypothermia and unilateral selective antegrade cerebral perfusion: a contemporary cerebral protection strategy for aortic arch surgery. *Ann Thorac Surg.* 2010;90:547– 54.] [19: Bakhtiary F, Dogan S, Dzemali O, Kleine P, Moritz A, Aybek T. Mild hypothermia (32°C) and antegrade cerebral perfusion in aortic arch operations. *Ann Thorac Surg.* 2006;132:153–4.] [20: Katz M, Khazin V, Steinmetz A, Sverdlov M, Rabin A, Chamovitz D, Schachner A, Cohen AJ. Distribution of cerebral flow using retrograde versus antegrade cerebral perfusion. *Ann Thorac Surg.* 1999;67:1065-9.] [21: Apostolakis E, Koletsis EN, Dedeilias P, Kokotsakis JN, Sakellaropoulos G, Psevdi A, Bolos K, Dougenis D. Antegrade Versus Retrograde Cerebral Perfusion in Relation to Postoperative Complications Following Aortic Arch Surgery for Acute Aortic Dissection Type A. *J Card Surg.* 2008;23(5):480-7.] [22: Usui A, Miyata H, Ueda Y, Motomura N, Takamoto S. Risk-adjusted and casematched comparative study between antegrade and retrograde cerebral perfusion during aortic arch surgery: based on the Japan Adult Cardiovascular Surgery Database:the Japan Cardiovascular Surgery Database Organization. *Gen Thorac Cardiovasc Surg.* 2012;60:132-9.] [23: Qian H, Hu J, Du L, Xue Y, Meng W, Zhang EY. Modified hypothermic circulatory arrest for emergent repair of acute aortic dissection type a: a single-center experience. *J Cardiothorac Surg.* 2013, 8(1): 125.] [24: Okita Y, Miyata H, Motomura N, Takamoto S, Japan Cardiovascular Surgery Database Organization. A study of brain protection during total arch replacement comparing antegrade cerebral perfusion versus hypothermic circulatory arrest, with or without retrograde cerebral perfusion: Analysis based on the Japan Adult Cardiovascular Surgery Database. *J Thorac Cardiovasc Surg.* 2015;149(2 Suppl):S65-73.] [25: Apaydin AZ, Islamoglu F, Askar FZ, Engin C, Posacioglu H, Yagdi T, Ayik F. Immediate clinical outcome after prolonged periods of brain protection: retrospective comparison of hypothermic circulatory arrest, retrograde, and antegrade perfusion. *J Card Surg.* 2009; 24:486-9.] [26: Hiraoka A, Chikazawa G, Totsugawa T, Sakaguchi T, Tamura K, Yoshitaka H. Acute Kidney Injury After

Total Aortic Arch Repair with Moderate Hypothermic Circulatory Arrest. *J Card Surg.* 2014;29(2):218-24.] [27: Roh GU, Lee JW, Nam SB, Lee J, Choi JR, Shim YH. Incidence and risk factors of acute kidney injury after thoracic aortic surgery for acute dissection. *Ann Thorac Surg.* 2012 ;94(3):766-71.] [28: Kato A, Ito E, Kamegai N, Mizutani M, Shimogushi H , Tanaka A. Risk factors for acute kidney injury after initial acute aortic dissection and their effect on long-term mortality. *Ren Replace Ther.*2016, 2(1):53.]

Since lower-body circulatory arrest is needed during ACP, organs in the lower body such as the viscera and spinal cord are still at risk of ischemia. Moderate hypothermia is still required to extend the tolerance of organs to anoxia, which may prolong CPB duration for cooling and rewarming. Lower-body circulatory arrest may therefore be a direct factor contributing to post-operative adverse events. To reduce the risk of ischemic injury to these organs, the viscera and spinal cord should be well perfused during opening distal anastomosis.

Retrograde inferior vena caval perfusion (RIVP) is a strategy used to provide the lower body with oxygenated blood. No venous valves are present in the visceral vein[[endnoteRef:29](#)], which makes RIVP possible. Previous animal studies have revealed that RIVP may benefit the abdominal organs by maintaining continuity in circulation and providing adequate blood flow for oxygen delivery[[endnoteRef:30](#)]. However, the debate remains unsettled about the optimal RIVP pressure and the feasibility of simultaneous retrograde bi-caval perfusion at a nasopharyngeal temperature of 18 °C[[endnoteRef:31](#)]. It has been reported that simultaneous continuous retrograde perfusion through both the inferior and superior vena cava can protect organs at a rectal temperature of 20 °C and perfusion flow rate of 300-600 mL/min[[endnoteRef:32](#)]. We are unaware of subsequent studies focusing on RIVP. [29: Oohara K, Usui A, Tanaka M, Abe T, Murase M. Determination of organ blood flows during retrograde inferior vena caval perfusion. *Ann Thorac Surg.* 1994 ;58(1):139-45.] [30: Rao PV, Stahl RF, Soller BR, Shortt KG, Hsi C, Cotter KJ, Belleisle JM, Moran JM. Retrograde abdominal visceral perfusion: is it beneficial? *Ann Thorac Surg.*1995, 60(6):1704-8.] [31: Yasuura K, Takagi Y, Oohara Y, Takami Y. Total body retrograde perfusion during operations on the descending thoracic aorta. *J Thorac Cardiovasc Surg.* 1999, 118(3):559-61.] [32: Yasuura K, Ogawa Y, Okamoto H, Asakura T, Hoshino M, Sawazaki M, Matsuura A, Maseki T, Abe T. Clinical application of total body retrograde perfusion to operation for aortic dissection. *Ann Thorac Surg.*1992, 53(4):655-8.]

The available evidence suggests that ACP provides more physiological blood flow to the brain than RCP, while RIVP reduces the risk of lower body ischemia by providing venous-to-arterial blood flow. Therefore, we have designed a trial to test whether the combination of ACP and RIVP is feasible under moderate hypothermia during reconstruction of the aortic arch. Furthermore, we will investigate the hypothesis that combining ACP and RIVP is superior to ACP alone for TARS under moderate hypothermia.

Objective and hypothesis

The primary aim of this multicenter trial is to assess whether RIVP combined with ACP leads to better outcomes than selective ACP alone for patients undergoing TARS (Protocol no. 1.0, dated 10 January2018) under moderate hypothermia. We hypothesize that combining RIVP with ACP will lead to

lower incidences of mortality, major complications and postoperative temporary neurological defects than ACP alone, as well as shorter duration of ventilation and stay in the intensive care unit (ICU). The results of this trial will serve as a foundation for future clinical recommendations regarding the application of RIVP in TARS and potentially improve treatment.

Methods

Study design

This study is designed as a multicenter, randomized, controlled, double-blind trial. Five clinical research centers in China will participate: West China Hospital of Sichuan University, First Affiliated Hospital of the University of South China, Second Affiliated Hospital of Nanjing Medical University, First Affiliated Hospital of Wannan Medical University, First Affiliated Hospital of the University of South China, and the Second Xiangya Hospital of Central South University.

A total of 500 participants with type A aortic dissection will be randomly assigned by computer to either the MHCA (control) group or RIVP group (n = 250 in each). Patients assigned to the control group will receive selective ACP alone under moderate hypothermia, while patients in RIVP group will receive selective ACP combined with RIVP under moderate hypothermia. Details of the trial have been published elsewhere[[endnoteRef:33](#)]. Patients will be monitored during a follow-up of one year to determine outcomes of surgical treatment. All patients will be admitted to a cardiovascular ICU after surgery, where they will remain until they are considered stable enough to transfer back to a general unit. Patient enrollment is expected to start on January 2019 and to be completed within 2 years thereafter. The following members of the study will be blinded to patients' group allocation: patients themselves, investigators, outcome assessors, the data manager, and the statistician. [[33: Lin J, Xiong J, Luo M, Tan Z, Wu Z, Guo Y, Du L. Combining cerebral perfusion with retrograde inferior vena caval perfusion for aortic arch surgery. Ann Thorac Surg. 2018 Oct 4. pii: S0003-4975\(18\)31356-0. \[Epub ahead of print\].](#)]

All perfusionists and surgeons in the trial will be experienced in performing necessary procedures. Interventions will be carried out during surgery, and follow-up visits will continue for one year afterwards. In addition, patients' medical records will be reviewed for in-hospital complications and medication usage.

This protocol was designed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines for interventional trials[[endnoteRef:34](#)]. The SPIRIT Checklist is shown in Additional file 1, and the SPIRIT Figure is shown in Figure 1. Participating centers will be required to sign a collaboration contract that lays out the responsibilities, intellectual property ownership, and publication processes. The funding for this trial covers only organizational costs and meetings; there is no third-party funding support for this trial. Changes to the protocol will be submitted to our ethics committee with a detailed description of the changes before going forward. All on-going severe adverse events (SAEs) will be followed up and documented until final outcomes are determined. [[34: Chan AW, Tetzlaff JM, Gøtzsche PC, Mann H, Berlin JA, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR.](#)

]

Ethics and registration

The protocol of this study follows guidelines set by the Declaration of Helsinki and is in accordance with the Medical Research Involving Human Subjects Act (WMO) as well as Good Clinical Practice guidelines[[endnoteRef:35](#)]. Central ethical approval has been confirmed from the Biomedical Ethics Committee of West China Hospital (ref approval no. 201824) and we will not begin recruiting at other centers in the trial until local ethical approval has been obtained. This trial has been registered at the Clinical Trial Registry (NCT.03607786). All results will be presented with the CONSORT (Consolidated Standards of Reporting Trials) statement (Figure 2). [[35: Guideline For Good Clinical Practice E6 \(R1\)](#)]. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 1996]

Recruitment of study population

The target study population is all patients aged 18 years or older diagnosed with AAAD and scheduled for elective or emergency TARS under CPB between January 1, 2019 and December 31, 2020. Participants will be recruited from the cardiovascular wards or ICU based on their presence on surgical lists. Eligibility will be assessed by surgeon fellows in the same hospital using thoracoabdominal enhanced computed tomography. Informed consent to participate will be obtained after a researcher has clearly explained to patients the trial and potential risks associated with RVP. Those who meet the selection criteria and give consent will provide demographic and general medical data as described below in the section "Baseline study visit".

Patients will be excluded from the study if they are unable to understand or give informed consent, if they are pregnant, or if they are already participating in another clinical trial that might interfere with the primary or secondary outcomes of the present trial. Patients will be withdrawn from the study if they are converted to another non-TARS procedure with no requirement for circulatory arrest, or if they or their agents/guardians revoke consent. Patients who withdraw from the study will not be replaced. Withdrawals will be documented in the electronic case report form (eCRF). The investigator can decide to withdraw a participant from the study for urgent medical reasons.

Data collection and management

All data will be recorded on a paper-based case report form (CRF). After in-hospital data are recorded, a trained assessor will enter the clinical data from the paper CRF into a web-based database. All participating centers, as well as the principal investigator, will have 24-hour access to the eCRFs. If data are entered incompletely or incorrectly, the principal investigator can contact the participating centers for further clarification. All outcome parameters will be recorded by a member of the trial team at each center at the time of enrolment and throughout the follow-up period. All trial data will be stored on a secure

server at the data coordinating center, kept secure and confidential, and retained for 15 years after completion of the study (defined as 365 days after follow-up of the last patient) and will be anonymized if requested by the authorities. Parameters critical to the primary aim of this trial will be monitored remotely.

Baseline study visit

As part of the baseline visit, we will collect patient information including age, height, weight, European System for Cardiac Operative Risk Evaluation (EuroSCORE II)[endnoteRef:36], smoking and drinking status, diabetes mellitus, peripheral arterial disease, lipid profile, pulmonary and cardio-cerebral co-morbidity, and pulmonary infection during the preceding 30 days. Preoperative hematology and biochemistry assessments will also be performed, including full blood count, electrolytes, liver and renal function tests, coagulation profile, thyroid function tests, and C-reactive protein. Enhanced thoracic and abdominal computed tomography and transthoracic echocardiography will be performed to confirm the preoperative diagnosis, measure left ventricular function, and detect valvular disease or other pathologies that meet the exclusion criteria. Additional clinical and study data collected at baseline, as well as at other study time points, are shown in Figure 1. [36: Nashef SA1, Roques F, Sharples LD, et al. EuroSCORE II. Eur J Cardiothorac Surg. 2012;41(4):734-44.]

Randomization and blinding

Patients will be randomly assigned to a group after anesthesia by an independent statistician uninvolved in the trial using a computer-generated randomization list. An equal number of patients will be allocated to the control and RVP groups at each center. The outcome of randomization will be displayed on a website accessible only to the independent statistician and the perfusionist. The allocation will be sealed in opaque envelopes prepared by an authorized trial coordinator at the coordinating center and distributed to the participating sites as needed. In cases when exclusion criteria are met after randomization (e.g. if total arch replacement is not performed), the patient will be withdrawn from the trial but will retain his or her identification code (randomization number).

Since the treatment allocation involves a surgical procedure, the surgeon, perfusionist and anesthesiologist will not be blinded to patient allocation. Physicians interacting with patients outside the operating room will be blinded to treatment allocation. The details of the randomization will be kept confidential until completion of data analysis.

Experimental intervention protocol

The CPB circuit will be set up according to a protocol described in our previous study³³. Briefly, the circuit consists of a membrane oxygenator, a heat exchanger, and two rolling pumps, which can bifurcate the arterial line for both artery perfusion and inferior vena caval perfusion as necessary. For patients in the RVP group, moderate hypothermia (defined as a nasopharyngeal temperature of 26-28 °C and rectal temperature of 28-30 °C) will be induced under CPB, then systemic perfusion will be stopped and the

aorta opened. ACP and RIVP will then be performed using the two rolling pumps. ACP will be performed with a starting pump flow rate of 6-12 mL/min/kg, which will be adjusted to maintain a mean arterial pressure of 40–60 mmHg. RIVP will be performed at a flow rate of 5-12 mL/min/kg and perfusion pressure below 25 mmHg. Ascites can occur when capillary pressures are above this perfusion pressure cut-off 30. Systemic perfusion will be restored after the aortic graft is sutured to the proximal end of the descending thoracic aorta. All patients in the study will undergo transesophageal echocardiography before and after bypass to observe blood flow in the liver and kidney during RIVP.

Patients in the control group will be perfused according to previously published methods[[endnoteRef:37](#)], [[endnoteRef:38](#)]. Briefly, the patient will be cooled slowly to induce moderate hypothermia (defined as a nasopharyngeal temperature of 24-26 °C and a rectal temperature of 26-28 °C) under CPB, after which ACP will be performed using the same perfusion pressure and flow as described above. RIVP will not be performed. [[37: Vallabhajosyula P, Jassar AS, Menon RS, Komlo C, Gutsche J, Desai ND, Hargrove WC, Bavaria JE, Szeto WY. Moderate Versus Deep Hypothermic Circulatory Arrest for Elective Aortic Transverse Hemiarch Reconstruction. *Ann Thorac Surg.* 2015; 99\(5\): 1511-7.\] \[\[38: Leshnowar BG, Kilgo PD, Chen EP. Total arch replacement using moderate hypothermic circulatory arrest and unilateral selective antegrade cerebral perfusion. *J Thorac Cardiovasc Surg.* 2014;147\\(5\\):1488-92.\]\(#\)\]](#)

Study outcomes

The primary outcome will be combined early mortality and major complications, including paraplegia, postoperative renal failure, severe liver dysfunction, postoperative prolonged intubation (>48 h), and gastrointestinal complications. Prolonged intubation will be defined as a requirement of intubation lasting more than 48 h. Other complications will be defined according to the Society of Thoracic Surgery (<https://www.sts.org/>). The primary outcome will be measured throughout hospitalization (regardless of length of stay) and for up to 30 days after surgery if the patient is discharged. Early mortality will be defined as any death that occurred in the same hospital in which the surgery was performed.

Secondary outcomes will include the proportion of patients with a stroke/cerebrovascular incident, paraparesis, temporary neurologic deficit, myocardial infarction, acute kidney injury not requiring dialysis, surgical re-exploration for bleeding, and deep sternal wound infection. Tertiary outcomes include the length of ICU stay, length of hospital stay, length of endotracheal intubation, volume of perioperative blood product transfusions, as well as total hospitalization cost. The proportion of patients who develop postoperative ascites will serve as a measure of safety in this trial.

Monitoring of adverse and clinical events

Intraoperative data will include variables linked to the arterial cannulation site for cerebral perfusion (cephobranial, internal carotid, axillary, or subcalvian artery), duration of HCA, CPB time, warming and cooling time, cross-clamp time, surgery time, temperature at the initiation of hypothermic circulatory arrest, concomitant procedures and application of cross clamp to the dissected aorta before initiation of hypothermic circulatory arrest, number of units of packed red blood cells, fresh-frozen plasma, pooled

platelets and cryoprecipitate administered perioperatively, the highest lactate value during CPB, and the highest flow and pressure of RIVP.

Patients will be monitored on a daily basis for 7 days after surgery to collect data on temperature, partial pressure of oxygen (PaO₂), inspiration O₂ (FiO₂), ventilation mode, hemoglobin and leukocyte count, and volume of chest drainage. Symptomatic cardiorespiratory complications and other secondary outcome measures (see above) will also be recorded during routine diagnostic tests. These parameters and the timing of notable events will be tracked until hospital discharge.

Patients will be instructed to visit the hospital at 30 days, 3 months, 6 months, and 12 months following discharge for postoperative data collection. If a face-to-face appointment is not possible, follow-up will be completed over the phone. During each visit, patient characteristics including mortality, cardiovascular and cerebrovascular events, postoperative renal and liver function, and gastrointestinal complications will be recorded on the CRF. In addition, radiology and electrocardiography will be performed at each visit, uploaded to the database and evaluated by outcome assessors blinded to patient allocation.

Pre- and postoperative data will be recorded by a member of the research team at each participating center who is blinded to randomization status and who is not part of the surgical team that performed the intervention. Intraoperative data will be collected by the study perfusionists and anesthesiologists.

Safety and monitoring

An independent data and safety monitoring board organized by cardiovascular surgeons, anesthesiologists and statisticians will oversee the progress and safety of the study, including adverse events and morbidity. All adverse events will be evaluated for severity. Any SAEs will be recorded on the CRF and reported within 24 h to the board and the Biological and Medical Ethics Committee of West China Hospital.

All unexpected major cardiovascular, cerebrovascular and other serious adverse events not listed in the protocol will be reported to the coordinating center within 24 h. The chief principal investigator will be responsible for all adverse event reporting. All adverse events will be closely followed until resolution or stabilization. A local investigator will review all reports of adverse events.

Data management and quality control

All CRFs will be immediately entered into a secure web-based system hosted by the data coordinating center as soon as they are received. Designated research team members will be authorized to access the allocation system and electronic CRFs by entering the patient's unique participant identification number, initials and date of birth in an online form. If data are entered incompletely or incorrectly, the principal investigator will contact the participating centers for clarification.

To control the quality of this study, all perfusionists will receive centralized training before the trial begins. All stored records will be kept secure and confidential according to standard guidelines. A reason must be

indicated whenever data are altered, and all alterations will be saved.

Sample size calculation

Based on the results of our previous study, we predict the incidence of the primary outcome to be 59.4% in the control group and 46.3% in the RIVP group. Patients will be evenly divided into two groups. The trial is planned to have 80% power with a two-sided type I error rate of 5%. Taking into consideration a dropout rate of 10% over the course of the entire study, we calculated a total sample size of 500 according to the following statistical formula.

Data analysis

Data analysis will be performed by a statistician using SPSS 20.0 (IBM, Chicago, IL, USA). Differences associated with $p < 0.05$ will be considered statistically significant. Continuous variables will be expressed as mean \pm standard deviation or median (interquartile range), and differences in such variables will be analyzed using an independent t test or the Wilcoxon signed-rank test, depending on whether data are normally distributed. Categorical variables will be described as numbers (percentages), and differences in such variables will be analyzed using chi-squared and Fisher's exact tests. Kaplan-Meier curves and log-rank analysis will be used to compare inter-group differences in primary and secondary outcomes. Univariate and multivariate logistic regression will be performed to determine relative risk of primary and secondary outcomes in the RIVP group compared with the control group.

Timeline 2018-2019: Development of research strategy and study protocol

2019-2020: Recruitment and treatment of patients in RIVP-TARS trial

2020-2021: Completion of follow-up and data analysis.

Discussion

Trial rationale

Improvements in CPB strategies, including selective cerebral perfusion and temperature management, have led to lower incidence of neurological dysfunction and other complications during the period of circulatory arrest than with DHCA. However, few studies have examined CPB improvement strategies aimed at visceral and lower-body perfusion. We and others propose that maintaining the continuity of lower-body blood flow may be important for avoiding visceral organ dysfunction and post-operative mortality[[endnoteRef:39](#)],[[endnoteRef:40](#)],[[endnoteRef:41](#)],[[endnoteRef:42](#)]. [[39](#): Hajjar L A, Almeida J P, Fukushima J T, Rhodes A, Vincent JL, Osawa EA, Galas FR. High lactate levels are predictors of major complications after cardiac surgery. *J Thorac Cardiovasc Surg.* 2013;146(2):455-60.] [[40](#): Mak NT, Iqbal S, Varennes BD, Khwaja K. Outcomes of post-cardiac surgery patients with persistent hyperlactatemia in the intensive care unit: a matched cohort study. *J Cardiothorac Surg.* 2016, 11(1):33.] [[41](#): Achouh PE, Madsen K, Miller CC 3rd, Estrera AL, Azizzadeh A, Dhareshwar J, Porat E, Safi HJ. Gastrointestinal

complications after descending thoracic and thoracoabdominal aortic repairs: A 14-year experience. *J Vasc Surg.* 2006, 44(3):442-6. [42: Yamashiro S, Arakaki R, Kise Y, Kise Y, Inafuku H, Kuniyoshi Y. Management of visceral malperfusion complicated with acute type A aortic dissection. *Interact Cardiovasc Thorac Surg.* 2015, 21(3):346-51.]

Distal perfusion through the descending aorta or femoral artery has previously been used to minimize damage to organs[[endnoteRef:43](#)],[[endnoteRef:44](#)]. However, this technique is associated with risk of poor occlusion, which seriously interferes with the operating field and leads to false lumen perfusion during femoral artery cannulation. Increasing perfusion through the inferior vena cava may help preserve visceral function and improve TARS outcomes, especially since the viscera lack venous valves. [43: Guo J, Wang Y, Zhu J, Cao J, Chen Z, Li Z, Qian X. Right axillary and femoral artery perfusion with mild hypothermia for aortic arch replacement. *J Cardiothorac Surg.* 2014, 9(1):94.] [44: Goda M, Suzuki S, Yabu N, Goda M, Machida D, Masuda M. Intermittent distal perfusion shortens hypothermic circulatory arrest time in aortic arch replacement surgery. *Gen Thorac Cardiovasc Surg.* 2017, 65(4):239-41. Figure 1. Schedule of enrollment, intervention, and assessment according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement. Figure 2. Flow chart of the RIVP trial.]

Our trial will combine ACP and RIVP during TARS using independently controlled upper- and lower-body perfusion circuits. This trial is expected to provide up-to-date data on the safety and efficacy of RIVP in patients undergoing TARS and has the potential to reduce the incidence of circulatory arrest-associated complications and perioperative blood product transfusion of AAAD patients, ultimately improving long- and short-term prognosis.

Trial status We are currently completing the electronic CRF system. The study will open to patient recruitment on 1 January 2019. Completion of this trial is expected in December 2021.

Declarations

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Availability of data and materials

Not applicable

Authors' contributions

LD and JL designed the study and helped draft the manuscript. DYK assisted with statistical consideration in the study design and analyzed the data. YQG, ZW, XLH, HY, DFZ, YZ and ZXT were involved in designing the study and reviewing the manuscript. YQG, ZW, JYX, BD, XSZ, ZW, YQ and YGF will participate in patient recruitment and data collection. JL and ZXT will assist with organization of study visits and monitoring. All authors read and approved the final version of this manuscript.

Ethics approval and consent to participate

The clinical trial is being conducted in line with the Declaration of Helsinki. The study protocol has been approved by the Biological and Medical Ethics Committee of West China Hospital (2018 trial number 24). All patients must be informed about the trial and give written informed consent in order to be enrolled.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Figures

TIME POINT	STUDY PERIOD						
	Enrollment	Allocation	Post-allocation				Closeout
	Day -1-0	Day 0	Inpatient	POD 30	Month 3	Month 6	Month 12
ENROLLMENT:							
Eligibility screen	×						
Informed consent	×						
Allocation		×					
INTERVENTIONS:							
ACP+RIVP		×					
ACP+MHCA		×					
ASSESSMENTS:							
Demographic data	×						
Medical history	×						
Concurrent medication	×						
Euroscore II	×						
Blood sample	×		×				
Cannulation site		×					
CPB data		×					
Volume of blood products		×	×				
Mortality			×	×	×	×	×
Paralysis			×	×	×	×	×
Visceral complications			×	×	×	×	×
Cerebrovascular complications			×	×	×	×	×
Cardiorespiratory complications			×	×	×	×	×
Reoperation			×				
Length of endotracheal intubation			×				
Length of ICU stay			×				
Length of hospital stay			×				
Total hospitalization cost			×				
Ascites			×				

Figure 1

Schedule of enrollment, intervention, and assessment according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.

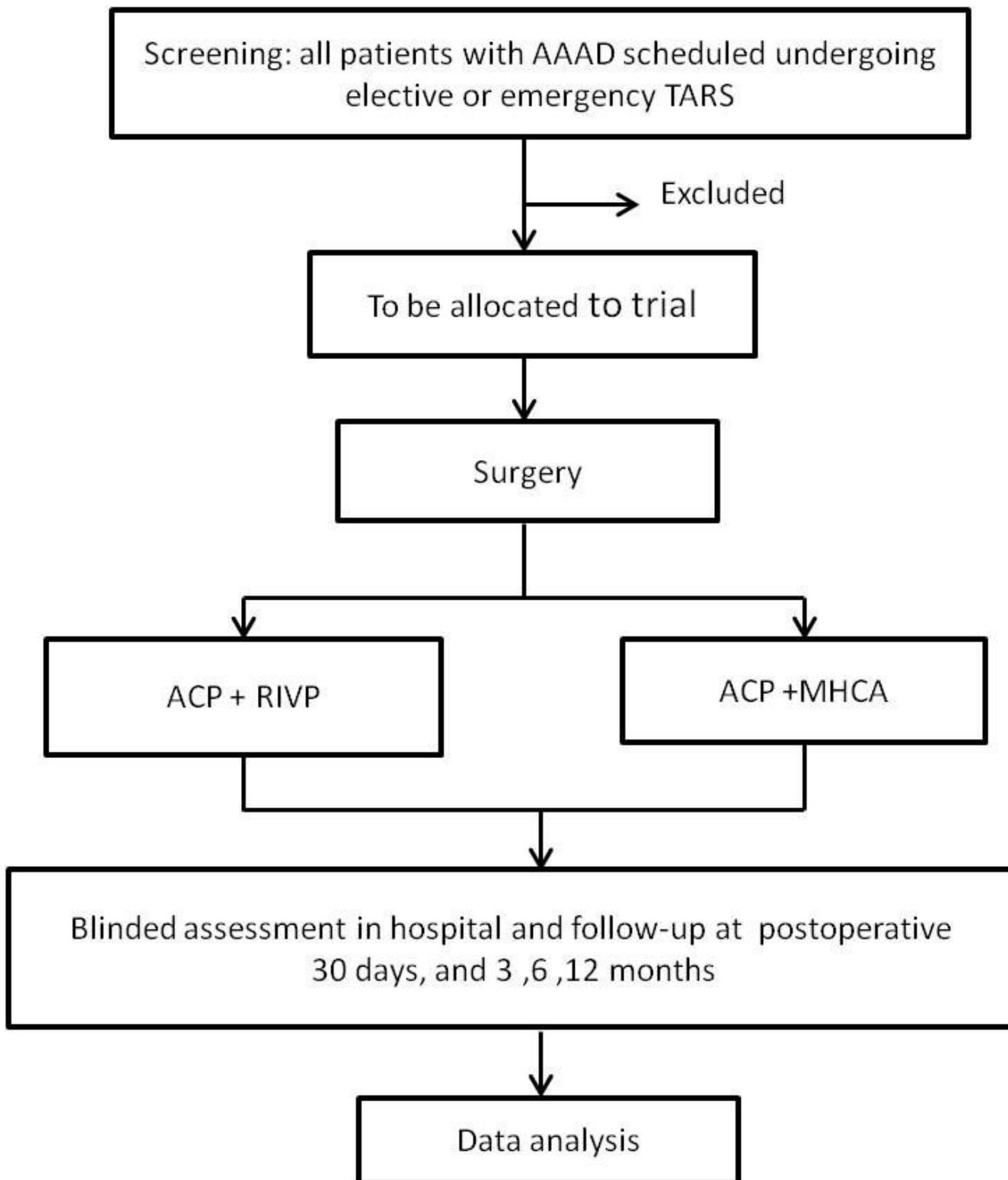


Figure 2

Flow chart of the RIVP trial.

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