SCA NEWS
SOCIETY OF CARDIOVASCULAR ANESTHESIOLOGISTS
Knowledge • Care • Investigation
Volume 38, Number 22
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PRESIDENT'S MESSAGE

Kathryn E. Glas
MD, MBA, FASE
President
Society of Cardiovascular Anesthesiologists

Greetings SCA Members!

I hope you have successfully navigated the global pandemic and are healthy and enjoying the new normal. Virtual content creation is ubiquitous, and we have learned how to plan hybrid meetings. SCA University is thriving, and our colleagues continue to generate excellent content for members. Be on the lookout for board review materials from the Program Directors group as you begin studying for the ACTA exam in December. All the content on SCA University, including CME materials, is free for society members.

"I foresee a bright future for our Society."

During the 2023 SCA Annual Meeting, the gavel was passed, literally, to the next Executive Committee. Thank you to **Dr. Stan Shernan** for your many years of service to the Society, and congratulations for the much-deserved Lifetime Achievement Award.

Dr. Shernan steps away from his role as Immediate Past President, and I am grateful he has agreed to remain active in the Society as a member of the International Council. Thank you to **Dr. Andy Shaw** for two years of stellar leadership of our Society; we look forward to your ongoing role as Immediate Past President.

Dr. Amanda Fox was selected as President-Elect, and we welcome **Dr. Doug Shook** to the team as Secretary/Treasurer.

I foresee a bright future for our Society with this intelligent, strategic, and thoughtful team leading the way.

Best Regards,

Kathy

2024 SCA MEETINGS

SCA Echo

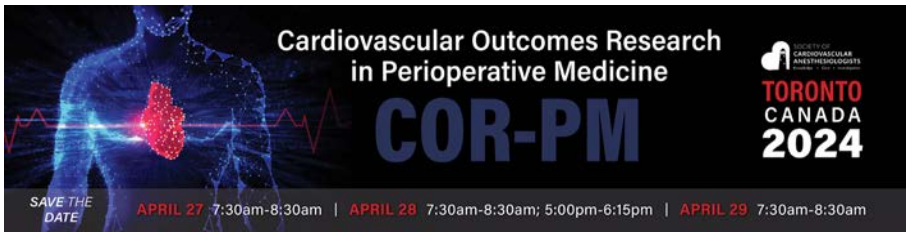
February 15-18

Thoracic Anesthesia Symposium & Workshops

April 26

Cardiovascular Outcomes Research in Perioperative Medicine

April 27-29



SCA Annual Meeting & Workshops

April 27-30

Echo Board Review Course

June 1-2

Don't miss out on these upcoming meetings!

2024 Call for Nominations is NOW Open!

Apply Today for an SCA Leadership Position

Submissions Close Monday, September 25, 2023

The opportunity is NOW if you want to play an integral role in shaping the future of the Cardiovascular Anesthesiology profession. **Eligible nominees must be an SCA "Active" Member in good standing.** The SCA seeks nominations for the following positions:

Director-at-Large (2 openings)

Term: 3-year term commencing in April 2024.

Overview: The Director-at-Large will bring expertise in cardiovascular anesthesiology, governance, and finance to the Board.

- The ideal candidate will have prior SCA involvement experience.
- Must attend up to 4 Board meetings per year.

Early Career Board of Director (2 openings)

Term: 2-year term commencing in April 2024.
Nominee must be within ten years of completing Fellowship training.

Overview: The Early Career Board Members will be voting members of the SCA Board of Directors.

- The ideal candidate will have had some previous involvement with SCA.
- Must attend up to 4 Board meetings per year.

Continuing Medical Education (CME) Committee Member (1 opening)

Term: Up to a 4-year term commencing in April 2024.

Overview: The CME Committee leads and facilitates the independent development of unbiased, scientifically balanced, CME activities.

- The ideal candidate will have prior SCA involvement experience.
- Must be able to attend up to 2 CME Committee meetings.

All nominees for any of the positions listed above must submit the following:

- A self-nomination letter or a letter of nomination from a Society member (for self-nominees, this letter cannot be combined with the statement of intent).
- Two letters from Society members seconding the nomination.
- A statement of intent from the nominee.
- The nominee's curriculum vitae.
- Biography – **150 words or less** (Those more than 150 words will be returned for revisions)
- A high-resolution, color business photo of the nominee.

If you are self-nominating or submitting your application:
Please complete the online application. Your SCA username and password is required.

CLICK HERE **TO SUBMIT YOUR APPLICATION**

If you are nominating another SCA member:
Please submit your letter of nomination to committees@scahq.org.
Submissions are due by 11:59 pm (Eastern) on Monday, September 25, 2023.
Newly elected leadership will be required to attend the Annual Meeting April 27-30, 2024.

Questions? Call us at 855.658.2828 or email committees@scahq.org.

***Please Note:** To be eligible to vote in the upcoming elections that opens in January 2024, SCA membership must be in good standing.*

Deadline for submissions is Sept 25th

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The SCA Mission Statement has been modified:

"Transforming perioperative cardiovascular and thoracic care through education, research and global collaboration."

2024 – 2026 Term Selection

Call for Volunteers Opens October 1st!

Consider volunteering for a SCA committee or sub-committe

Support your Society's strategic goals and initiatives by serving on one of its 40-plus committees and sub-committees! The Call for Volunteers will be open October 1 – 31, 2023 for the 2024-2026 term. Watch your in-box for details!

The following committees are anticipated to have openings:

- Abstract Review Committee
- Acute Kidney Injury (AKI) Sub-Committee
- Blood Management Sub-Committee
- Clinical Practice Improvement Committee
- Cardiovascular Outcomes Research in Perioperative Medicine (COR-PM) Program Planning

Committee

- Echo Week Program Planning Committee
- Economics and Gov. Affairs Sub-Committee
- Enhanced Recovery After Thoracic Surgery (ERATS) Sub-Committee
- Ethics Committee
- Guidelines and Standards Sub-Committee
- History Council
- International Committee
- Kaplan Leadership Development Award Sub-Committee
- Member Engagement Committee
- Newsletter Sub-Committee
- Online Education Sub-committee
- Quality, Safety and Value Committee (formerly QSL Committee)
- Research Committee
- SCA STS Database Sub-Committee
- Scientific Program Planning Committee (SCA Annual Meeting and Workshops)
- Thoracic Anesthesia Symposium and Workshops (TAS) Program Planning Committee
- Transplantation Sub-Committee

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PUF Research Award
Submit Your Letter of Intent NOW!

Due Date: August 22, 2023

SCA members are eligible to submit their Letter of Intent (LOI) for the 2nd Annual PUF Research Program. **The letter of intent deadline is August 22, 2023.**

PUF applications being accepted for research projects based on data from the Adult Cardiac Surgery Database, General Thoracic Surgery Database, Congenital Heart Surgery Database, and the INTERMACS Database.

All STS Database related documents are available after a free registration through the STS website: www.sts.org.

The letter of intent should include:
(All documents will be required to be uploaded as a PDF)

The Society of Thoracic Surgeons

- The Letter of Intent (LOI) should not be more than two pages.
- The LOI should detail the proposed title of the project and a statement that the PI/applicants checked and verified that their proposed work is not similar to a previously completed or presently active STS approved research proposal.
  - List of active STS research proposals from all programs
  - List of recently published STS research studies based on STS National Database data
- The LOI should describe the roles of the key personnel including PI, co-investigators, cardiac surgeon who are also an active STS member, and a PhD level biostatistician. Their backgrounds/connection to the topic area, the key personnel, and the unique skills or resources they and their institutions bring to the project.
- Details of the proposed study, including background, specific aims, the study design, and target patient population or disease process, along with a description of any translational/mechanistic components.
- Biosketch in the new NIH formatting for the PI.

Award Details:

- **Total award amount:** $60,000 for a total of 4 grants awarded at $15,000 each.
- **Award duration:** One time award.
- **Letter of intent (required) deadline: August 22, 2023.**
- Notification of invitation for full application: October 5, 2023.
- Application deadline for invited applicants: November 28, 2023.
- Award recipients announced: January 2024.
- Click Here for full application requirements.

***Please Note:** SCA will **not** consider applications from primary investigators (PI's) currently receiving SCA research funding. However, they may serve as a co-investigator on a PUF application.*

The PUF award is essential for us as a society, and to ensure SCA's first year of success, please circulate within your network.

CLICK HERE **TO SUBMIT YOUR LETTER OF INTENT BY AUGUST 22, 2023.**

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2024 Kaplan Leadership Development Award — Accepting Applications Beginning September 15!

The 2024 Kaplan Leadership Development Award application submission window will open September 15, 2023. The award is designed to assist cardiothoracic and vascular anesthesiologists in their career by granting funding to further their leadership development through coursework and leadership-specific studies.

The Kaplan Leadership Award will be adjusted accordingly to offer an aggregate of $5,000 to either one recipient or divided among two.

- **$5,000/$2,500 from the SCA Endowment, with a $5,000/$2,500 match from the applicant's institution to fund a leadership education strategy.**

CLICK HERE

For more information regarding the Kaplan Leadership Development Award and how to apply.
The deadline to submit your application is January 15, 2024.

Questions about the grant and grant application should be emailed to operations@scahq.org, or via telephone at 855.658.2828.

CARE
INVESTIGATION
KNOWLEDGE

SOCIETY OF CARDIOVASCULAR ANESTHESIOLOGISTS
ENDOWMENT

Support Your Society through the SCA Endowment

SCA is the preeminent international educational organization for this sub-specialty, leading the way in treatment innovations through care, investigation, and knowledge. By donating to the SCA Endowment, the funds help support SCA professionals to further their education, research, and professional development and to achieve their goals.

The SCA Endowment Fund online donation page is available. Making an online donation is quick, easy, and secure. To complete the online donation form, visit www.SCA Endowment.

Vision of the SCA Endowment

We will be world leaders in enhancing patient care and safety and in developing excellence in the next generation of clinicians and physician-scholars through research and education in the field of cardiothoracic and vascular anesthesia.

For more details on the endowment, please email donation@scahq.org.

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Checkout this New Podcast

NEW EDUCATIONAL PODCAST!

SCA UNIVERSITY
An Online Learning Management System

7-part Educational Podcast Series is now available in the SCA University!

The SCA Quality, Safety and Value (formerly QSL) Committee in collaboration with the Society of Thoracic Surgeons, has developed an educational series on the Society of Thoracic Surgeons Adult Cardiac Surgery Database (STS ACSD). This 7-part Educational Podcast Series is now available in the SCA University!

The STS ACSD database is relevant to SCA Members, cardiac anesthesiology fellows, and practicing cardiac anesthesiologists. It can be utilized in collaboration with their cardiac surgical team to do quality assessments and develop quality improvement projects.

Accreditation Statement The Society of Cardiovascular Anesthesiologists is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The Society of Cardiovascular Anesthesiologists designates this enduring material activity for a maximum of 2.75 ***AMA PRA Category 1 Credits.***™ Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This course is for **FREE** to all SCA members within the SCA University account! If you have not created an account, you will need to do so before you can access. If log in assistance is required, please contact **info@scahq.org.** For non-members, you can join and have access to this compelling series.

CLICK HERE

Still Time to Register for the ICCVA-CASSA Meeting

2023 ICCVA-CASSA CONGRESS

Towards Safe Cardiovascular and Thoracic Surgery Outcomes

30 November – 2 December 2023

The 19th International Congress of Cardiothoracic and Vascular Anesthesia in conjunction with the CASSA-JPC Congress

Century City Conference Centre, Cape Town, South Africa

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New Member Benefit

ABA REVIEW COURSE

Check out the short video that explains the availability and usage of the ABA Board Review Content that is NOW available on the SCA LMS.

CLICK HERE TO VIEW THE SHORT VIDEO

SCA's ARC: A Review Course for the Adult Cardiac Anesthesia Board Examination will be administered by the American Board of Anesthesiology for the first time in December 2023.

Three new modules added:

- Cardiomyopathy 1
- Cardiopulmonary Bypass: Neurologic, Metabolic and Endocrine Effects
- Cardiopulmonary Bypass (pharmacokinetics and pharmacodynamics)

This course is for **FREE** to all SCA members within the SCA University account! If you have not created an account, you will need to do so before you can access. If log in assistance is required, please contact **info@scahq.org**. For non-members, you can join and have access to these interactive modules!

CLICK HERE TO ACCESS THE COURSE

Our review course embraces the intersection of technology and education and hosts a series of 36 interactive modules that will walk you through the content outline of the ACA exam. These modules contain images, videos, tables, and text from a variety of sources, but have been arranged for members in easy-to-navigate modules. Work through our modules that are rigorously cited and peer reviewed. This release is just Part 1 of what the SCA will offer for its review course, with the remaining 7 modules coming soon.

Additional Modules Coming Soon!

Topics that will be covered:

- Aortic Stenosis
- Cardiac Catheterization 1
- Cardiac Catheterization 2
- Cardiac Output
- Cardiac Tamponade
- Cardiopulmonary Bypass (hematologic effects)
- Cardiopulmonary Bypass (myocardial preservation, cardiothoracic & respiratory effects)
- Cardiopulmonary Bypass (renal effects)
- Cardiopulmonary Bypass (thermoregulatory effects)
- Coagulation
- Conduction System
- Congenital 1
- Congenital 2
- CSF Drains and SSEPS
- ECMO
- Embryology
- Heart Transplant
- Hypertrophic Cardiomyopathy
- IABP
- Infiltrative Storage Disease
- Ischemic Heart Disease
- Lung Isolation
- LVAD
- Mitral Regurgitation
- Mitral Stenosis
- Neoplastic Disease
- Pacemakers & AICDs
- Pericardial Surgery
- Post-operative Left Ventricular Failure & Inotropes
- Post-operative Right Ventricular Failure & Vasodilators
- Pulmonary Artery Catheter
- Pulmonary Regurgitation and Stenosis
- Right Ventricular Assist Device
- TAAA
- Tricuspid Regurgitation and Stenosis

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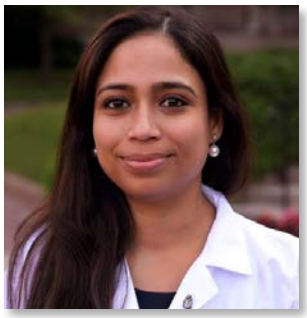

Samhati Mondal, MBBS, MD, FASE
Associate Professor
Department of Anesthesiology
University of Maryland School of Medicine
Baltimore, MD

(A commentary on 'Racial Disparities in Compensation Among US Anesthesiologists: Results of a National Survey of Anesthesiologists' by Vandenberg et al published in Anesthesia & Analgesia: DOI: 10.1213/ANE.0000000000006484) subcommittee of DEI.

DEI COMMITTEE

Racial and Ethnic Disparity in Physician Anesthesiologists' Compensation — Well-Known Gap Yet to be Closed!

Lack of parity among physicians' compensation based on gender and races has been well-documented.[1] Anesthesiology is no exception. As we are moving forward to a more inclusive path and attempting to close the gap, this disparity in compensation is a major hurdle that needs to be addressed. Physicians' wellbeing including financial wellness, is crucial for them to be more productive and able to deliver high quality care with improved physician patient relationship.[2] A high intensity specialty like anesthesiology where rate of burn out and attrition is so high even in early career[3], a lower compensation based on race and ethnicity despite equal training and amount of working hours is morally upsetting and adds fuel to the situation.

A recent study by Vandenberg and Milam et al. shed light on this critical concerning issue.[4] Although multiple studies have shown racial disparities in pay among physicians, this is the first of its kind that was done among practicing full-time anesthesiologists in USA. Anesthesiology is a distinct specialty in medicine and data from national database studies done in primary care fields cannot be extrapolated and generalized to apply to anesthesiologists. Hence, Vandenberg's study focusing on anesthesiologists was not only important, but was very much needed. Authors conducted the study based on national survey that was originally planned to look at lack of equity in pay based on gender by ad hoc committee of American Society of Anesthesiologists (ASA), Women in Anesthesia (AHCWIA) in 2018. However, the data demonstrated scope of further sub analysis of anesthesiologists' compensation-based on race and ethnicity as well, given the sample size and information related to ethnicity and race. Survey was sent to 28,000 ASA members and 1,952 observations were analyzed after implementing inclusion and exclusion criteria.

Authors primarily categorized racial groups into two sub-groups – non-Hispanic White (77.8%) and anesthesiologists from racial and ethnic minority group (22.2%) to mitigate inadequate power due to smaller sample size in the latter group if they were to be individually categorized (black, Hispanic, Asian Indian, Asian non-Indian, Alaskan native, Native Hawaiian). In their final statistical regression models, authors adjusted for various plausible confounders including gender, age, spousal work status, US Census region, weekly hours worked, taking call, practice type, academic rank, and completion of fellowship.

This study showed, after adjusting for all the confounders, anesthesiologists belonging to ethical and racial minority group have 26% lower odds of being in the higher compensation compared to non-Hispanic White counterpart (OR, 0.74; 95% confidence interval [CI], 0.61–0.91). This lower odd remained uniformly lower in minority group over six ranges of salary figures of 50 thousand dollars apart, starting from < $250,000 to $450,000-499,000. Compensation becomes same in minority and white groups when it reaches to the highest compensation i.e. > $500,000.

In a model including all 1,952 anesthesiologists, it showed a striking difference of $16,557 lower median compensation in the racial and ethnic minority group comparing with White anesthesiologists.

Further sensitivity analysis among underrepresented minority (URiM; black, Hispanic, Native Hawaiian, Alaskan native), non-Hispanic Asians and non-Hispanic White, demonstrated Asians are at significantly higher risk of not receiving higher compensation comparing with non-Hispanic White (OR, 0.71; 95% CI, 0.56–0.90). This association among URiM and non-Hispanic White were not statistically significant though (OR 0.80; 95% CI, 0.59–1.08). This finding of higher odds among Asian anesthesiologists not being compensated with higher pay comparing with White anesthesiologists is concerning since Asians consist of 20% of physician workforce in USA(5), including 15% of anesthesiologists as quoted in this study.

As authors demonstrated, there is a lack of equitability in compensation among anesthesiologists in USA, based on race and ethnicity despite adjusting for gender, professional rank, spousal working condition, practice type and length and type of training. This lack of parity is concerning and we as a professional society must address this issue with utmost priority. Because physician anesthesiologists' financial well-being will impact their service and morality and consequently, quality of care they will deliver to patients. I applaud authors for conducting the study and highlighting this disparity in the compensation structure so that effective measures can be taken toward building an equitable pathway.

References

1. Larson AR, Englander MJ, Youmans QR, Verduzco-Gutierrez M, Stanford FC, Strong SA, et al. Analysis of Physician Compensation Studies by Gender, Race, and Ethnicity. *Health Equity.* 2022;6(1):59-71.
2. Menacker M. Physician Compensation Methodology Must Change! *Am J Med.* 2019;132(5):554-5.
3. Rothschild L, Ward C. Early-Career Physician Burnout. *Anesthesiol Clin.* 2022;40(2):315-23.
4. Vandenberg MT, Kraus M, Misra L, Hertzberg L, Buckner-Petty S, Padmanabhan A, et al. Racial Disparities in Compensation Among US Anesthesiologists: Results of a National Survey of Anesthesiologists. *Anesth Analg.* 2023;137(2):268-76.
5. Bailey V. AAMC: Gender and Racial Diversity On the Rise in US Physician Workforce: RevCycleIntelligence; 2023 [Available from: https://revcycleintelligence.com/news/aamc-gender-and-racial-diversity-on-the-rise-in-us-physician-workforce.

AWEsome Woman Interview

Nancy A. Nussmeier, MD

Current: Physician Editor in Anesthesiology at UpToDate™
Most recent academic appointments: Cardiac Anesthesia Staff, Massachusetts General Hospital, Department of Anesthesia, Critical Care and Pain Medicine, Boston, MA
Prior: Professor and Chair, SUNY Upstate Medical University Syracuse, NY

Introduction: I I am currently employed as a Physician Editor in Anesthesiology at *UpToDate*™. Until recently, I also worked at Massachusetts General Hospital (Boston). I previously held positions as Professor and Chair of the Department of Anesthesiology at SUNY Upstate Medical University (Syracuse), Director of Cardiovascular Anesthesia Research at the Texas Heart Institute (Houston), and as a cardiac anesthesiologist at the University of California San Francisco. After graduating from Purdue University and then Indiana University School of Medicine, I completed my residency in Anesthesiology at Massachusetts General Hospital, and fellowship in Cardiac Anesthesia at Emory University (Atlanta).

Over the years, my research has been widely published in peer-reviewed journals and I have contributed to several medical textbooks. I also served on several editorial boards and as the Associate Editor-in-Chief for Anesthesia & Analgesia Case Reports. Previous national positions outside of the SCA include service on the American Heart Association Leadership Council for Cardiovascular Surgery and Anesthesia, the FDA Anesthetic and Life Support Drugs Advisory Committee, and Chair of the American Society of Anesthesiologists Educational Track for Cardiac Anesthesia.

1. What led you to become a Cardiovascular/Thoracic Anesthesiologist?
I loved witnessing and participating in the life-and-death physiological and technical challenges and the innovations that happened every day in the cardiac operating room.

2. How did you hear about the SCA?
In 1984, I was encouraged to join by three advisors: a faculty member during my fellowship at Emory University (John Waller, MD), my research mentor at Texas Heart Institute (Stephen Slogoff, MD), and a Chief of Cardiac Anesthesia that I met at the ASA (Jerry Reves, MD). All were SCA members.

3. What roles have you held for the society?
2015-Present – Endowment Council member
2007-2018 - Vice-Chair, Board of Directors, SCA Foundation
(precursor to the Endowment Fund and Council)
2000-2006 - SCA Board of Directors
2003-2007 - Chair, Research Committee

4. What is one of your greatest achievements as a Cardiovascular/Thoracic Anesthesiologist?
Clinical research in several areas including:
a. Cerebral protection during cardiac surgery with CPB
b. Gender-related outcomes after cardiac surgery
c. Patient safety in the cardiac operating room

5. Do you have any advice for fellows and residents?
Recognize or create opportunities to reinvigorate a satisfying career by sharpening or changing your professional focus over time. Strive to improve your own professional excitement and satisfaction, knowledge in your field, your patients' care, success of your younger colleagues, or some combination of these motivating factors.

6. Have you experienced any difficulties as a woman in the field?
In all honesty, I believe it was a significant advantage in my era.

7. Do you have any advice for other women in the field?
Although you will undoubtedly be faced with particularly challenging and exhausting periods of time, these should be temporary. Don't let go of important aspects of your personal life (especially relationships with children and other important people in your life), even as you try to build and maintain a satisfying career.

8. How do you balance work and personal life?
Put professional responsibilities and family responsibilities first. But maintain one or more hobbies, take reasonable time off, and stay healthy. (During selected periods of my life and career, I opted to sacrifice salary for academic time, personal time, or both. Those were good decisions.)

9. What is something you enjoy doing outside of work?
Horseback riding in wilderness areas. (Some biking, hiking, and skiing, but mostly horseback riding.) Reading (print and audio books), theater, museums, restaurants. (So much to do – so little time!)

10. Would you change anything about the path you took to get to where you are now?
I made several changes in my career with respect to professional focus, job title and responsibilities, institutions, and geographical locations. This worked well for me but would not be optimal for everyone. Developing depth and breadth in the same institution has been an equally good or better strategy for many of my colleagues.

11. What was the best piece of advice you received?
From my father, who noticed my "workaholic" lifestyle, not unlike his own: "No one lies on their deathbed saying to themselves 'I wish I had worked harder'."

Check Out the SCA History Timeline!

Learn about the history of the Society of Cardiovascular Anesthesiologists, from 1976 to today!

CLICK HERE

To View the Timeline

Check Out the Swag!

The New SCA Swag Store is Here!

SCA branded t-shirts, sweatshirts, mugs, and more are now available for purchase!
Start shopping today by clicking on the link below.

CLICK HERE

To View the SCA Store

Don't Miss Out —
RENEW YOUR MEMBERSHIP TODAY!

You are a valued member of the SCA community. Do not miss out on all the NEW member benefits! Continue receiving your SCA benefits uninterrupted by renewing today.

Renew Online – You can login to your membership account to pay your dues online with the option to enroll in auto renew.

If you have any questions about your membership or the renewal process, please contact the SCA Team at 855.658.2828 or **info@scahq.org.**

SOCIETY OF CARDIOVASCULAR ANESTHESIOLOGISTS
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LITERATURE REVIEWS

Prognostic Impact of Right Ventricular Strain in Isolated Severe Tricuspid Regurgitation

Hinojar, R., et al. (2023). "Prognostic Impact of Right Ventricular Strain in Isolated Severe Tricuspid Regurgitation." J Am Soc Echocardiogr 36(6): 615-623. doi: 10.1016/j echo.2023.02.009

Reviewers:

Jose Gallegos, MD
Anesthesia Resident, PGY-3
NYU Grossman School of Medicine

Liliya Pospishil, MD
Assistant Professor
NYU Grossman School of Medicine

Background

Significant tricuspid regurgitation (TR) has been shown to be associated with an increased morbidity and mortality.[1] Despite increasing evidence of the unfavorable nature of severe isolated TR, its management remains challenging. Medical therapy for severe TR provides symptom relief without improving survival. Isolated tricuspid valve surgical intervention is often done after end-organ damage has already occurred, with morality up to 10%.[2] The current American Heart Association/American College of Cardiology (AHA/ACC) guidelines provide only a weak (class 2b) recommendation for surgical intervention for isolated TR in the presence of progressive dilation or systolic dysfunction.[3] However, the AHA/ACC acknowledges the ongoing research investigating the evaluation, timing, and mode of intervention. Recent studies have started to shed light on the potential benefits of transcatheter tricuspid valve intervention (TTVI) on morbidity and mortality with regards to stratified right ventricular (RV) function.[4] Although the authors highlight that RV function is an important determinant of outcomes and prognosis in patients with isolated TR, they argue that the conventional methods (fractional area change, tricuspid annular plane systolic excursion, and RV S' wave) for identifying RV dysfunction have limitations in identifying early RV dysfunction. Speckle tracking echocardiography (STE) is a newer technique which quantifies cardiac strain, and is able to overcome the shortcomings (reproducibility, angle/load dependence) of conventional evaluation methods.[5] RV strain has been shown to hold prognostic relevance for those with severe TR.[6] Therefore, the authors aimed to examine whether RV strain (using STE) is more sensitive in identifying early RV dysfunction and holds more prognostic value than standard echocardiographic parameters in asymptomatic patients with severe isolated TR.

Methods

This study is a single-center prospective observational study of consecutive patients with isolated, asymptomatic, secondary, severe TR undergoing evaluation in the Heart Valve Clinic from 2016-2019. The median follow-up period was 26 months. Exclusion criteria included: previous heart failure (HF), significant left heart disease or presence of alternative cause of RV remodeling. Transthoracic echocardiographic (TTE) parameters of RV function were acquired via RV-focused four-chamber view and included RV fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), and RV S' velocity. RV global longitudinal strain (GLS) and free wall longitudinal strain (FWLS) were recorded using STE analysis with artificial intelligence to define endocardial border limits. Abnormal RV FWLS values were defined as those > -20%, but no defined threshold was used for GLS. Right atrial (RA) pressure/volume and left ventricle ejection fraction were also collected from TTE data. The combined endpoints were hospitalization for heart failure and death. Aside from standard comparison of means and categorical data, multivariable Cox analysis was used to determine independent associations with outcomes for the collected data variables.

Results

A total of 151 patients fit inclusion criteria and completed the entire follow-up period. 83% had severe TR and 17% had massive or torrential TR. Ninety-one percent were classified NYHA functional class I or II. The etiologies observed were functional ventricular TR (48%), atrial functional TR (40%), cardiac implantable device-related TR (8%), and primary TR (4%). Fifty-three patients (35%) reached the combined end point (1 of which died). Those who had events were found to have more severe TR, larger RV diameters, larger RV end-diastolic and -systolic areas, higher RA volumes, and worse RV strain ($p<0.5$ for all). There was no significant difference with regards to TAPSE, S' wave, and FAC measurements between those with and without events. In those with normal values of TAPSE, S' waves, and FAC, FWLS was impaired in 39% of patients.

Only RV FWLS, biplane vena contracta (VC), and NYHA functional class remained independent predictors of HF and mortality after multivariable analysis. The adjusted hazard ratio for those with an abnormal FWLS was 5.90 (CI, 3.17-10.99; p<0.001). Based on receiver operating characteristic (ROC) curve analysis, an adjusted cutoff value of >-21.5% for FWLS demonstrated the best accuracy for predicting outcomes. When analyzing the subgroup with normal RV function based on conventional indices, FWLS remained an independent predictor of events with the adjusted cutoff value previously listed (HR, 3.5; 95% CI, 1.6-6.99; p=0.001).

Discussion

The authors were able to demonstrate that RV strain can be used as a reliable indicator of early RV dysfunction in patients with at least severe TR. Additionally, their findings suggest that conventional measurements of RV function may not be sufficient in identifying early RV dysfunction in the setting of severe TR. The incorporation of STE to identify RV strain may also serve as a prognostic indicator for developing HF and mortality in those with severe TR.

Recent studies have failed to show improved survival following surgical intervention compared to those managed medically.[7] However, majority of the patients undergoing surgical intervention already have signs of overt HF. The question remains whether similar results would be observed if earlier intervention was implemented. In a later study, catheter-based interventions for severe TR were studied and a mortality benefit was observed only in those with mid-range reduced RV function.[4] The RV function was defined based on TAPSE-derived measurements. Given that this study demonstrated a lack of sensitivity using this parameter, it would be relevant to further explore outcomes with RV strain-defined categorization in those undergoing TTVI.

In addition to being performed at a single center, the study's limitations include small sample size and the use of non-validated cut-off values for wall strain. Despite incorporating RV GLS without a predefined range for normal values, the authors were still able to support their hypothesis with RV FWLS data alone. Lastly, three-dimensional echocardiography has recently been observed to hold similar diagnostic value when evaluating right heart function and was not included in the study.[8]

Despite these limitations, this study is a valuable contribution to the literature evaluating prognostic parameters in severe tricuspid regurgitation. RV strain has emerged as a promising tool in identifying early RV dysfunction and may help with deciding on the most appropriate time of tricuspid valve intervention.

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Minithoracotomy vs Conventional Sternotomy for Mitral Valve Repair: A Randomized Clinical Trial

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Background

Mitral valve repair is the ideal first line surgical intervention for mitral regurgitation, as it is associated with better survival than mitral valve replacement.[1] Repair has traditionally been performed via sternotomy, necessitating sternal immobilization that delays return to presurgery physical function for at least 12 weeks. In recent years, minimally invasive thoracoscopic techniques have been growing in demand among patients and favored as a durable alternative to traditional sternotomy. Minimally invasive approaches have offered benefits in improved cosmesis, less surgical pain, and better patient satisfaction.[2] It has also been theorized that the lack of sternal immobilization may allow for faster recovery to presurgery quality of life, which has been shown to be an important outcome to patients.[3] Despite this rising interest in minimally invasive repair, only one randomized clinical trial has compared sternotomy to thoracoscopic techniques. This study found the levels of mortality and need for reoperation were similar between the two groups, implying that the standard of care was met in the noninvasive group.[4] However, this study was limited in that it was a single center study that specifically looked at patients with Barlow disease.[4] The current study thus represents the first multicenter RCT comparing the two procedures, as well as the first to investigate the outcome of return to function.

Methods

This multi-center, randomized control trial was a superiority trial between Mini thoracotomy (intervention) and sternotomy (control). The primary outcome was physical function and activity measured using the SF-36 physical function scale. Secondary outcomes, including mitral regurgitation grade, physical activity levels, and quality of life were also measured, as well as safety outcomes including mortality, need for repeat surgery, and heart failure hospitalization. Participants included adult patients with mitral regurgitation requiring mitral valve repair. Patients could still participate in the study if they were having concurrent procedures on the tricuspid valve or for atrial fibrillation, but those having additional surgery on the aortic valve or coronaries were excluded. Each procedure was performed by surgeons considered an "expert" in that surgical technique, defined as over 50 logged procedures. Outcomes were analyzed with T-scores using a linear mixed-effects model to adjust for variables.

Results

330 patients passed screening criteria and were enrolled in the study, with 309 eventually undergoing surgery (147 in the sternotomy group vs 162 in Mini thoracotomy). There was no difference in the primary outcome of change in baseline in SF-36 physical function scores at 12 weeks (7.62 vs 7.20). Similarly, there was no difference in the number of patients with mitral regurgitation grades of none or mild at 12 weeks (95% vs 96%) or at one year (92% vs 92%). There was a slight improvement in daily vigorous exercise time at 6 weeks for the Mini thoracotomy group (favored by 9.97 minutes), but this difference was no longer significant by 12 weeks post-surgery. The median length of stay postoperatively was decreased by 1 day in the Mini thoracotomy group (5 days vs 6 days). There was no difference in quality-of-life scores at any time point. Safety metrics including mortality, reoperation, stroke, and hospitalization for heart failure were similar between the two groups at 12 weeks and one year.

Discussions

This is the largest RCT to date comparing minimally invasive technique against sternotomy for mitral valve repair. It is also the first to investigate function and quality of life as outcomes, as previous studies primarily examined mortality, morbidity, and recurrent mitral regurgitation. The

results of the study suggest that there is no significant difference in the outcomes of return to function or residual mitral regurgitation post-operation between the two surgical pathways when performed by expert surgeons. Additionally, there was no difference in terms of safety in the form of mortality, re-operation, or hospitalization for heart failure exacerbation. Any RCT exploring a difference between minimally invasive surgery and a sternotomy would necessarily be limited in that it is impossible to blind patients to the type of procedure they have, which may create bias in survey results. Additionally, this study may have limitations in its generalizability to other surgical centers that may lack experts who perform one or both procedures. More study is likely warranted to ensure reproducibility, but the results suggest that Mini thoracotomy performed by a trained surgeon meets the standard of care set by sternotomy for mitral valve repair. 12 weeks (7.62 vs 7.20). Similarly, there was no difference in the number of patients with mitral regurgitation grades of none or mild at 12 weeks (95% vs 96%) or at one year (92% vs 92%). There was a slight improvement in daily vigorous exercise time at 6 weeks for the Mini thoracotomy.

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FOCUS TOPIC: ARTIFICIAL INTELLIGENCE AND ECHOCARDIOGRAPHY CLINICAL INVESTIGATIONS
Fully Automated Artificial Intelligence Assessment of Aortic Stenosis by Echocardiography

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Background
Artificial intelligence (AI), as an emerging innovative technology has been studied in some applications of echocardiography for fully automated echocardiographic interpretation[1] of the assessment of the systolic and diastolic function[2] or measurement of global longitudinal strain.[3] The echocardiographic application of a machine learning methodology without manually derived TTE measurements for the evaluation of aortic stenosis, has not been evaluated yet.

The deep- learning algorithms developed by Us2.ai, allow AI driven automatic interpretation of the echocardiogram and became FDA approved, after validation at the Harvard/ Brigham and Women's Hospital Echo Core Lab. Echocardiographic measurements including volumes of the cardiac chambers, ejection fraction or Doppler measurements, derived by deep learning, were compared with those obtained by human experts and excellent agreement was demonstrated. Additionally, in cohort of echocardiograms, deep learning of Us2.ai algorithms automatically annotated 2D videos and Doppler tracings just as accurately as the measurements performed by expert sonographers.[2]

Algorithms for automatic assessment of aortic stenosis (AS) have been created for Us2.ai but their accuracy has not been assessed and they have not been validated. In this study Us2.ai derived measurements of the aortic valve (AV) peak velocity (Vmax), AV velocity time integral (VTI), AV mean pressure gradient (MPG), left ventricular outflow tract (LVOT) diameter (LVOTd), LVOT VTI, stroke volume index (Svi) and AV area (AVA) were obtained. The accuracy of the above measurements was assessed by comparing them with the measurements done by expert echocardiographers.

The measurements were performed by 3 trained echocardiographers. The measurement of the LVOT diameter and the final adjudication for discordant values were done by 2 level III echocardiographers. All readers were blinded to the values from the AI measurements. The continuity equation was utilized for the manual or AI based calculation of the AVA.

De-identified transthoracic echocardiograms were uploaded in the Us2.ai platform and the measurements were obtained automatically. Manual and automated values were analyzed using Pearson's correlation. $P<0.05$ was considered statistically significant.

Results
As shown from the correlation coefficients and P values, strong positive correlation and agreement was found between manual and AI measurements for the values used in the continuity equation and the calculation of the AVA:

LVOT VTI (r = 0.89, P < .001), AV VTI (r = 0.96, P < .001), LVOTd (r = 0.76, P < .001) and AVA (r = 0.88, P < .001).

Strong correlation was also demonstrated between AI and human measurements of the Svi (r = 0.79, P < .001), Vmax (r = 0.97, P < .001) and MPG (r = 0.94, P < .001).

High interobserver agreement was demonstrated among the readers. The agreement among the measurements was similar across all grades of AS.

Illinois in Chicago were included. In the 256 randomly selected studies, 94 had no AS, 53 had mild AS, 63 moderate and 46 severe. Patients with bicuspid or prosthetic AO valve were excluded.

Discussion

Aortic stenosis is the most common valvular heart disease in the elderly.[4] Patients with severe AS have a 25.6% all-cause mortality in 2 years.[5] Accurate diagnosis and grading of AS is very important for appropriate risk stratification and management. In the population of patients with AS, AI has recently been assisting in the development of algorithms that incorporate other parameters such as age or gradient or diastolic function and was found to correlate better with outcomes than AVA alone.[9,10] The above algorithms require manual calculation of the AVA.

The algorithms developed for the Us2.ai neural platform enable the automated calculation of the AVA, from an echocardiographic study uploaded to the platform.

Further development of this application will enable diagnosis of AS and calculation of the AVA in the absence of personnel with more specialized training than image acquisition.

Refining of this promising modality is needed: As seen in the study results, the value with the highest variability was the LVOTd. Because the LVOTd is squared in the continuity equation, it can lead to discrepancies in the AVA estimation. This was likely observed because the algorithm incorporates in the measurement all LVOT views and not all are always optimized vs the experienced reader used the most appropriate clip make the measurement. Also, all Doppler envelopes seen are used by the machine for the measurement of the VTI. The experienced reader will exclude the VTI post ectopy, but the machine will not.

Despite the limitations mentioned, artificial neural platforms, have the capacity to mimic expert human echocardiography readers and will likely transform the way we practice and use echocardiography in the future.

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Association of Right Ventricular Functional Parameters with Adverse Cardiopulmonary Outcomes: A Meta-analysis

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Background

Right ventricular dysfunction is a significant contributor to perioperative morbidity and mortality, regardless of its underlying etiology.[1] It is an associated comorbidity in roughly 10% and 25% of hemodynamically unstable patients intra- and postoperatively.[2] Early diagnosis of right ventricular dysfunction may lead to more timely initiation of management with resultant improved prognosis. Conversely, delayed diagnosis or a missed diagnosis may contribute to significant morbidity and mortality.[1] On two-dimensional (2D) echocardiography, right ventricular (RV) function is commonly assessed using tricuspid annular plane systolic excursion (TAPSE), fractional area of change (FAC), and/or free- wall longitudinal strain (FWLS).[3] However, given the complex triangular and crescent-shaped geometry of the RV, these 2D metrics may not fully capture right ventricular dysfunction.[4] The aim of this study was to determine if assessing RV ejection fraction (RVEF) using 3D echocardiography was superior to 2D echocardiography parameters (TAPSE, FAC, FWLS) in its association with adverse cardiopulmonary outcomes and all-cause mortality.

Methods

This study was a meta-analysis of English-language, peer-reviewed studies evaluating the association between RVEF on 3D echocardiography and clinical outcomes. Accepted studies included at least 20 adult patients and reported all-cause mortality and/or adverse cardiopulmonary outcomes as hazard ratios (HR) per unit change of RVEF function as well as TAPSE, RV FAC, or RV FWLS. To facilitate comparisons across metrics, hazard ratios were standardized by rescaling against in-study 95% confidence intervals (CI). A pooled-effects model was used to generate an overall estimate of the association of RVEF with adverse outcomes, relative to other metrics. A ratio >1 is interpreted to mean that a 1 SD reduction in RVEF is related to a greater hazard increment relative to a 1 SD reduction in a comparative metric. Statistical heterogeneity was assessed and sensitivity analyses were performed to monitor the effect of small sample sizes Post-hoc analyses were performed to determine if baseline pulmonary hypertension diagnosis or study endpoint (mortality v. composite) accounted for heterogeneity. A pre-planned subgroup analysis compared the pooled HR estimates of studies evaluating cohorts with or without a primary diagnosis of pulmonary hypertension.

Results

This meta-analysis included 10 studies and a total of 1,928 patients. The mean (+/-SD) age of the patient population was 63 +/- 15 years. 46% were female. The follow-up duration ranged from 3 to 44 months. Three studies included patients with pulmonary hypertension exclusively. Other studies were limited to patients with COVID-19[1], dilated cardiomyopathy[1], aortic stenosis[1], and heart failure with preserved EF (HFpEF,[1]). Three studies included patients regardless of cardiovascular disease diagnoses.

394 patients (20.4%) suffered adverse cardiopulmonary events or mortality. A 1 SD reduction in RVEF was associated with a 2.64-fold (95% CI, 2.18-3.20, P < .001) increased risk of all-cause mortality and/or adverse cardiopulmonary events. 1 SD reductions in TAPSE, FAC and FWLS were

associated with hazard ratios of 1.81 [95% CI, 1.43-2.28]; 1.71 [95% CI, 1.44-2.02] and 1.77 [95% CI, 1.42-2.21], respectively. The HR per SD change for RVEF as a correlate of adverse outcomes was 1.54 (95% CI, 1.04-2.28, P = .031) times greater than that of TAPSE; 1.45 (95% CI, 1.15-1.81, P = .001) times greater than that of FAC, and 1.44 (95% CI, 1.07-1.95, P = .018) times greater than that of FWLS.

3D RVEF was strongly correlated with adverse outcomes regardless of pulmonary hypertension diagnosis, demonstrating hazard ratios of 2.97 [95% CI, 2.12-4.14] among patients with and 2.57 [95% CI, 2.04-3.24] among patients without pulmonary hypertension.

Discussion and Conclusion

In this large meta-analysis, RV dysfunction as measured by 3D RVEF, TAPSE, FAC and FWSI was strongly associated with increased risk of mortality and adverse cardiopulmonary events. However, RVEF measured on 3D echocardiography was significantly more sensitive in identifying patients with RV dysfunction at increased risk for poor outcomes. 1 SD reduction in 3D echocardiography derived RVEF showed a significantly stronger correlation with adverse events than did with a comparable change in TAPSE, FAC, or FWLS. This was observed in populations with and without pulmonary hypertension diagnoses. Limitations of this meta-analysis include nonuniform design and varying inclusion criteria of analyzed studies, requiring statistical control.

The ability to more sensitively recognize vulnerable patients is critical in crafting therapeutic interventions to reduce morbidity and mortality due to RV dysfunction. 3D RVEF may prove to be a useful clinical tool to refine or redefine perioperative cardiopulmonary risk stratification. Further investigation is warranted into this important topic.

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PRO CON

INTRODUCTION:
VASOPLEGIA

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Vasoplegia associated with cardiopulmonary bypass is type of vasodilatory shock with similarities to that seen in sepsis, adrenal insufficiency, and hepatic failure.[1,2,3,4,5] Although definitions vary, a general description includes reduced mean systemic arterial pressure (MAP), reduced systemic vascular resistance (SVR), normal or increased cardiac output or index (CO; CI), with or without the administration of a vasopressor.[1,2,3,4] More specifically, and for the purposes of the following 'Pro Pro' discussion, it will be defined as:

Mean Arterial Pressure < 60 mmHg
Cardiac Index > 2.2 L/min/m2
Systemic Vascular Resistance < 800 dynes x sec/cm5

Despite
Norepinephrine infusion > 0.1 ug/kg/min

Despite adequate fluid resuscitation and high dose norepinephrine patients remain hypotensive and exhibit a vascular hyporesponsive state. While most cases are self-limiting others may persist longer than 6-8 hours.

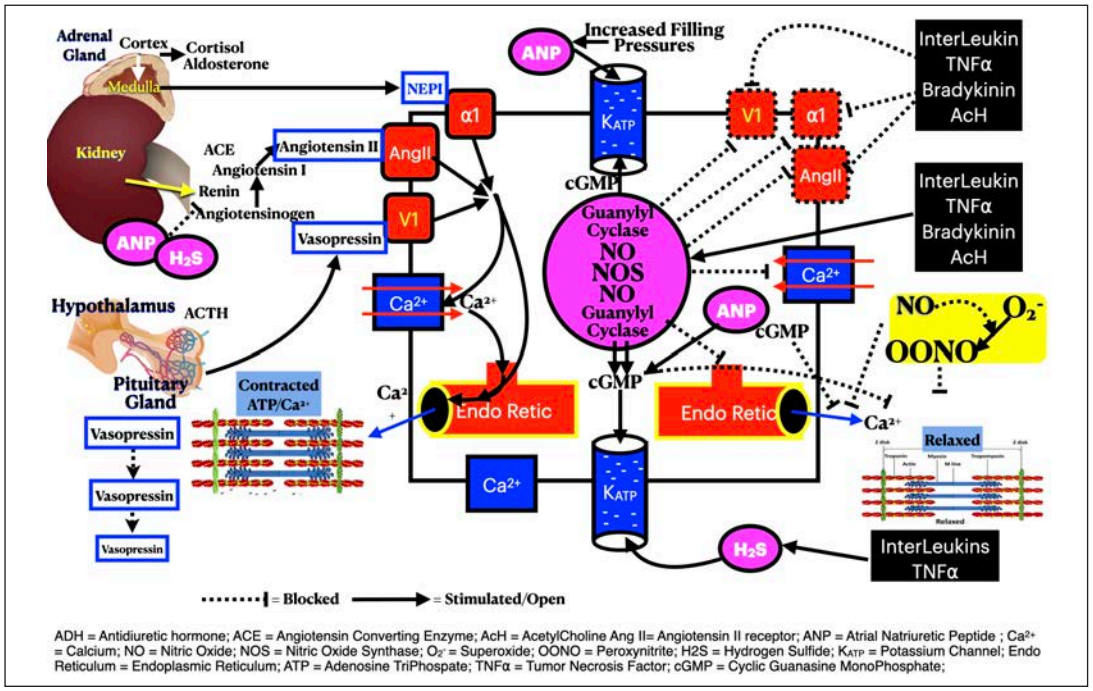
Vasoplegia occurs in up to 50% of cardiac surgical cases and may last for hours or days.[5,6,7] Multiple risk factors have been reported and include Euro risk score, preoperative infection, preoperative use of vasopressors, ACEi, ARB and heparin, renal failure, left ventricular systolic dysfunction, anemia, and increased aortic cross clamp and cardiopulmonary bypass time.[4,6,8,9,10,11] Prolonged vasoplegia is defined as persistent need for vasopressors and a catecholamine-hypo-responsiveness > 6-8 hours.[3,4,6,12] Prolonged vasoplegia after heart surgery is associated with end-organ hypoperfusion, renal, liver, and pulmonary dysfunction, metabolic acidosis, prolonged mechanical ventilation, prolonged ICU and hospital stay, and increased mortality. Severe systemic complications develop if the vasoplegic syndrome last > 36 hours.[12] The characteristics of vasoplegic syndrome are like those observed in septic shock, where the alterations are mediated by inflammatory mediator such as inflammatory cytokines and tumor necrosis factor-alpha.[12]

Several mechanisms are described prompting the exploration and application of alternative non-catecholamine therapies **(Figure 1)**. With regard to vasoplegia associated with cardiopulmonary bypass, the literature describing and guiding therapy is a collection of case reports, case series, and relatively few randomized studies supported by experimental data. Review articles combine data from cardiac surgical and non-cardiac surgical patients, e.g., sepsis, to describe therapies algorithms to manage refractory hypotension.

continued...

SOCIETY OF CARDIOVASCULAR ANESTHESIOLOGISTS
Knowledge • Care • Investigation

(Figure 1)



ADH = Antidiuretic hormone; ACE = Angiotensin Converting Enzyme; AcH = AcetylCholine Ang II= Angiotensin II receptor; ANP = Atrial Natriuretic Peptide ; Ca^{2+} = Calcium; NO = Nitric Oxide; NOS = Nitric Oxide Synthase; O_{2^-} = Superoxide; OONO = Peroxynitrite; H2S = Hydrogen Sulfide; K_{ATP} = Potassium Channel; Endo Reticulum = Endoplasmic Reticulum; ATP = Adenosine TriPhospate; TNFα = Tumor Necrosis Factor; cGMP = Cyclic Guanasine MonoPhosphate;

Mechanism of Vasodilation/Pathophysiology of Vasoplegia

Systemic vascular resistance is determined by arteriolar diameter, volume, and tone. Vasoconstriction occurs due to a rise of intracellular Ca2+ from the sarcoplasmic reticulum which interacts with the myofilaments of the vascular smooth muscle cell (VSMC) leading to contraction and vasoconstriction.[5] The influx of Ca2+ occurs after catecholamines bind -1 adrenergic receptors, arginine vasopressin (AVP) binds Vasopressin-1 receptors, or angiotensin II binds angiotensin type-1 receptors. VSMC relaxation occurs with the reuptake of Ca2+ into the sarcoplasmic reticulum, followed by return of normal transmembrane ionic gradients due to K+-Ca2+-ATPase pumps. A relaxed VSMC is accomplished by a hyperpolarized transmembrane state due to open potassium channels and higher intracellular/extracellular K+ gradient.

Nitric oxide (NO) is a critical factor of normal vascular function. NO is generated from L-arginine by three different synthase isoforms nitric oxide synthase (NOS) and inhibits contractility, cellular proliferation, and platelet activation. Nitric oxide diffuses freely into vascular cells and binds Guanylyl-Cyclase, which converts guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP). cGMP prevents calcium entry and interaction with myofilaments and stimulates calcium sequestration in the endoplasmic reticulum.[5] NO also activates KATP channels to enhance or create a hyperpolarized hyporesponsive cell membrane resulting in vasodilation.[5,13]

Inflammation and inflammatory cytokines increase calcium-dependent inducible NO synthase (iNOS) significantly increasing NO production and is a major driver of vascular shock, vasoplegia and redistribution shock.[13] Cardiac surgery and cardiopulmonary bypass cause inflammation due to surgical cell trauma, interaction with CPB tubing, and ischemia-reperfusion changes, placing the patient at risk for vasoplegia, with similarities to that of septic shock.[11,12] Inflammation causes the release of inflammatory cytokines including interleukins and tumor necrosis factor- , which in turn stimulates the production of NO from L-arginine, hydrogen sulfide from L-Cysteine, two mediators of vasoplegia, and VSMC hypo-responsiveness.[5,13]

Although NO synthase (NOS) and NO and H2S are major contributors toward the vasoplegic state, other factors contribute. Atrial natriuretic peptide (ANP) increases cGMP, which phosphorylates and activates cGMP-dependent protein kinases (PKG), causing Ca2+ sequestration and vasodilation and keeps KATP channels open resulting in membrane hyperpolarization.[2,6,14] ANP inhibits the renin-angiotensin-aldosterone-system and decreases sodium and water reabsorption.[2,6,14,15] Hydrogen sulfide (H2S) is increased with inflammation and activates KATP channels hyperpolarizing the cell membrane, reducing stimulation from vasopressors and vascular tone. Vascular hypo-responsiveness may be due to reduced centrally

in the hypothalamic-pituitary level, peripherally with altered or reduced adrenal gland activity and catecholamine production, by blunted baro- and chemo-receptors activity.[3]

Normally, angiotensin II triggers the adrenal glands to release aldosterone and stimulates the pituitary gland to release antidiuretic hormone (ADH, or vasopressin). During vasoplegia the hypothalamic-pituitary-adrenal axis is suppressed contributing toward hypotension and/or resulting in a blunted response to hypotension. Absolute or relative reductions in vasopressin levels and aldosterone production have been described.[4,16,17,18,19,20] Inflammation and cardiopulmonary bypass either cause or are associated with reduced vascular reactivity due to these reduced neurohumoral inputs, the effects of acidosis, ATP depletion, and hyperpolarization of membranes.[14] Catecholamine resistance and subsequent catecholamine depletion are either the result of these mechanisms and/or a contributor toward vasoplegia.[5,13]

Individually or together, these mechanisms cause vasodilation despite administration of catecholamines, i.e., vascular hypo-responsiveness.[11] This dysautonomia is accompanied by a loss of cardiovascular variability, inappropriate tachycardia, hypotension, and hypo-perfusion.[3] Continued stimulation of adrenergic receptors results in downregulation and reduction of membrane surface receptors and further hypo-responsiveness.[3,14,21,22] Hemodynamic management should address the primary causative problem, the initiating mechanism, and supportive therapies while the patient's system recovers. When considering the management of vasoplegia the selection of medications may be less important than the timing of appropriate therapy.[23] In an analysis 20 studies including 1,608 patients with vasoplegia due to sepsis (10/20 studies [50%]), cardiac surgery (7/20 [35%]), vasodilatory shock due to any cause (2/20 [19%]), and acute traumatic injury (1/20 [5%]) treatment with non-catecholaminergic agents improves survival.[23]

Although protocols and algorithms are described, refractory hypotension persists. First line therapies vary per practitioner, institution, and availability **(Table 1)**. While Vasopressin (FDA 2014) and Angiotensin II (Giapreza; FDA 2018) are FDA approved for refractory hypotension due to vasodilation, Methylene Blue and Hydoxycobalamin are used off-label.[1] In this 'Pro, Pro' intravenous Vasopressin, and Methylene Blue/Hydroxocobalamin are compared.

(Table 1)

	Site/Mode	Dose	Cost	Availability	Advantage	Disadvantage
Norepinephrine	$\alpha_1\ \alpha_2\ \beta_1$	0.01-3.0 ug/kg/min	$	Immediate	↑SVR Possible β1 Activity	↓responsiveness
Epinephrine	$\alpha_1\ \alpha_2\ \beta_1$	0.01-1.0 ug/kg/min	$	Immediate	↑MAP ↑ Inotrope	↓ responsiveness
Phenylephrine	$\alpha_1\ \alpha_2$	0.1-5.0 ug/kg/min	$	Immediate	↑ SVR	↓responsiveness
Dopamine	$\alpha_1\ \alpha_2\ \beta_1$ Dopaminergic Receptors	1-20 ug/kg/min	$	Immediate	↑ SVR ↑ Inotropy	↓esponsiveness Arrhythmias; ↑ PVR
Vasopressin (ADH)	V_1	0.01-0.2 U/min	$$	Immediate	↑ SVR ↑ Water Reab.	Splanchnic, Coronary Constriction
Angiotensin II	AT1	10-40 ng/kg/min	$$$$	Difficult/ Not Available	↑ SVR ↑Aldosterone ↑ ADH Secretion	Bronchoconstriction ProCoagulant
Methylene Blue	Multiple Receptors	1-3 mg/kg 0.25-0.5 mg/kg/hr	$$$	Immediate	Inhibit NO, NOS, Inhibit Guanylyl Cyclase Scavenge/Reduce NO	Green Urine; Pulse Ox Int. Serotonin Syndrome Hemolysis (G6PD def)
Hydroxycobalamin	Cbl/VB12 B12 Receptor	5-10 gm 200-500 mg/hr	$$$$	Orderable	Inhibit NO, NOS, H_2S Reduce/Scavenge NO Reduce H2S	Headache Photosensitivity
Vitamin C	Adrenal Gland Co-Factor SVCT2 Transporter	1.5 gm q6h	$$	Immediate	Improve Receptor Responsiveness Catecholamines Synthesis Reduce Vascular Permeability	Hyperoxaluria
Hydrocortisone	Adrenal Gland Glucocorticoid Receptor	50-100 mg q6h	$	Immediate	↑Catecholamine Synthesis Anti-Inflammaotry	Outcome data lacking Infection Risk
Thiamine	Thiamine Transporter	100 mg q6h	$$	Orderable	Convert Ascorbic Acid to Oxalate Improves Clearance of Lactate Reduces Cell Death	Rash Red Skin

ADH = Antidiuretic hormone; AT1 = Angiotensin 1; Cal = Cobalamin; SVCT2 = Sodium Dependent Vitamin C Transporter 2; SVR = Systemic Vascular Resitance; MAP = Mean Arterial Pressure; NO = Nitric Oxide; NOS = Nitric Oxide Synthase; H2S = Hydrogen Sulfide; G6PD = Glucose 6 Phosphate Dehydrogenase

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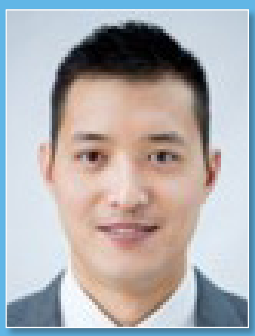
Vasopressin is the Best First-Line Treatment in Vasoplegia Syndrome



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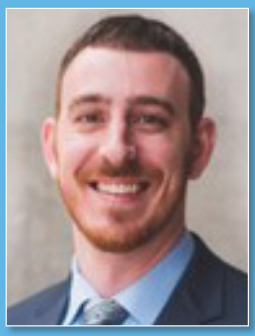

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Vasoplegia or vasodilatory shock is characterized by poorly controlled vasodilation with limited responsiveness to catecholamine vasopressors often accompanied by a metabolic acidosis.[1] Classically attributed to septic shock, this condition occurs in cardiac surgical patients with a perioperative incidence between 9% and 44%.[2] Norepinephrine-refractory vasoplegia is associated with up to 81% major morbidity and a mortality rate as high as 25% when the vasoplegia persists for more than 36 hours.[3] Given the catecholamine hypo-responsiveness, the use a non-catecholamine vasopressor as first-line therapy to correct vasoplegia is indicated.

The etiology of vasoplegia is multifaceted and therapy must counter the pathophysiology. Vasoplegic shock is primarily initiated by a systemic inflammatory response with release of inflammatory and cytokine mediators that cause vascular smooth muscle cell (VSMC) hypo-responsiveness to catecholamines i.e., dysautonomia.[4,5] Nitric oxide (NO) induced vasodilation is another contributor to the vasoplegic state, which is further worsened by decreased vasopressin levels systemically that also occurs in vasoplegia.[4,6] Particularly for vasoplegia associated with sepsis or cardiac surgery with CPB, vasopressin levels have been found to be low or lower than anticipated.[6,7,8] Compared to pre CPB baseline, vasopressin levels increase for the first 30 minutes of cardiopulmonary bypass, however, levels decline back toward baseline 15 minutes later.[8] In a prospective study of 145 patients undergoing cardiac surgery endogenous arginine vasopressin (AVP) levels were measured five minutes after weaning from CPB and a vasopressin deficiency was noted in patients with vasoplegia or vasodilatory shock.[9] Furthermore, serum levels of AVP increased with initiation of a vasopressin infusion suggesting that the decline was related to either reduced production or depletion of AVP but likely not secondary to metabolism.[6,7]

Vasopressin, also called the antidiuretic hormone (ADH), binds to three main receptors: V1, V2, V3.[10] V1 receptors are located on vascular smooth muscle cells, myocardial cells, platelets, and hepatocytes causing vascular constriction, cardiac hypertrophy, platelet aggregation, and glycogenolysis. Vasoconstriction occurs by signaling G-protein coupled with phosphatidylinositol to increase intracellular Ca2+ for myofilaments leading to contraction. V2 receptors are found on the renal collecting tubules and increase fluid reabsorption playing a critical role in maintaining blood pressure regulation and plasma osmolarity. Finally, stimulation of V3 receptors causes the release of corticotrophin releasing hormone from the hypothalamus to release Adrenocorticotrophin Hormone (ACTH) which increases cortisol production and release from the adrenal glands, necessary for normal catecholamine synthesis.

The vascular smooth muscle effects of vasopressin differ in the systemic and pulmonary circulations. Under normal physiologic conditions, nitric oxide synthase is stimulated via either V1 or V2 receptors with low serum levels of vasopressin resulting in pulmonary vascular dilation.[10,11,12] However, in an inflammatory state, when inflammatory and cytokine mediators stimulate smooth muscle cells, an infusion of vasopressin inhibits systemic vascular endothelial (eNOS) and inducible (iNOS) nitric oxide synthase, thus reducing NO production, and causing systemic vascular smooth muscle contraction and improving catecholamine responsiveness.[13,14,15] Additionally, infusion of vasopressin inhibits KATP channels, attenuating and preventing membrane hyperpolarization and its associated vasodilation.[15] In contrast, vasopressin either inhibits NOS in the pulmonary vasculature or has minimal effect on vascular tone making it the ideal systemic vasopressor for patients with pulmonary hypertension to increase the ratio between systemic and pulmonary vascular resistance.[10,11,12] This benefit has been observed with low-dose infusions of

vasopressin resulting in increased mean arterial pressures and decreased intravenous catecholamine requirements.[9,16]

While study outcomes vary when comparing norepinephrine (NE) with non-catecholamine vasopressors, vasopressin infusions have been shown to improve hemodynamics and reduce intravenous catecholamine vasopressor requirements. Additional reported benefits include improved renal outcome, reduced cardiac arrhythmias, and, in some reports, reduced ICU stay and improved survival.[4,16,17,18,19,20,21,22,23] The Vasopressin and Septic Shock Trial (VASST) was a multicenter randomized double-blind study in patients with septic shock that showed that addition of 0.01 to 0.03U/min of vasopressin to ongoing norepinephrine infusions resulted in significantly lower doses of norepinephrine when compared to norepinephrine infusions alone.[24] Although the Vasopressin vs Norepinephrine as Initial Therapy in Septic Shock (VANISH) trial, a double-blind-randomized control trial, did not demonstrate a lower incidence of renal failure, the vasopressin group was shown to have a decreased incidence of atrial fibrillation and higher rate of weaning from renal replacement therapy.[20] In a systematic review of 10 randomized control trials a reduced mortality was found with the use of vasopressin with norepinephrine compared to norepinephrine alone (RR 0.91; 95% CI 0.83-0.99).[25] In a review of 23 RCTs (21 of which included vasopressin; 2 Angiotensin II) involving 4380 individuals, non-catecholamine vasopressors, lowered the need for mechanical ventilation, improved renal function, and lowered 28-day mortality and among patients with refractory septic shock.[26]

The more recent VANCS trial was a randomized controlled investigation that compared vasopressin to norepinephrine in post-CPB vasoplegia.[27] Three hundred cardiac patients, who required vasopressor drugs for vasodilatory shock within 48 hours of weaning from CPB, were randomized in a 1:1 ratio to treatment with 0.01 to 0.06 U/min of vasopressin or 10 to 60ug/min of norepinephrine. The primary outcome, a composite endpoint of death or severe postoperative complications within 30 days after surgery, occurred in 74 patients in the norepinephrine group and in 48 patients in the vasopressin group (hazard ratio 0.55, p=0.0014). Vasopressin was associated with significantly less acute renal failure compared to norepinephrine (10.3% vs 35.8%, p<0.0001) and fewer patients in the vasopressin group required renal replacement therapy (2.7% vs 13.9%, p=0.0016). Incidence of atrial fibrillation was also lower in the vasopressin group (63.8% vs 82.1%, p=0.004). Interestingly, the duration of study-drug infusion was shorter in the vasopressin group when compared to the norepinephrine group (34 vs 57 hours, p=0.0003). All these differences, however, did not translate to a difference in mortality rate (15.9% vs 15.4%, p=0.98). There was no difference in digital, mesenteric, or myocardial ischemia/infarcts. The study supports use of AVP as a non-inferior first-line therapy and shows that AVP is associated with less incidence of arrhythmia and kidney injury.

The timing of administration of vasoactive medications may be important. In another study conducted among patients who had undergone cardiac surgery, the prophylactic perioperative (intraoperative to 4 hours postoperative) administration of 0.03 U/min of vasopressin was compared to placebo.[28] The vasopressin group recorded higher MAPs, and a lower incidence of (8 vs 20%) of perioperative vasoplegia as well as lowered mortality. In the postoperative period, superior hemodynamic data was recorded in the vasopressin group and a reduced requirement for catecholamine vasopressors (norepinephrine and epinephrine) was noted. When compared to the non-vasopressin group, the overall duration of infusion of vasopressors was also lower in the vasopressin group.[29] Ammar et al reported when vasopressin was administered within 4-6 hours to patients already receiving high dose norepinephrine > 0.1 ug/kg/min or 10-15 ug/min, hemodynamic goals were attained sooner and maintained with greater success.[29]

Lam et al assessed outcome and compared cost benefit analyses between norepinephrine, vasopressin, and angiotensin II in septic patients[30] Vasopressin given in addition to norepinephrine was the most cost-effective therapy and superior to norepinephrine alone,

and combined angiotensin II/norepinephrine mainly by increasing ICU survival.[31] Cost benefits were maintained when considering Quality Life Years (QALY) at a ratio of 19,762$/QALY gained.[30]

	ICU survival	Cost ($)	Quality Life Years
Norepinephrine alone	52	58,126	3.78
Norepi + Vasopressin	61	53,207	4.52
Norepi + Angiotensin II	54	59,681	3.95

Cost analysis comparing Norepinephrine alone or in combination with vasopressin and angiotensin II. Lam SW, Barreto EF, Scott R, Kashani KB, Khanna AK, Bauer SR. Cost-effectiveness of second-line vasopressors for the treatment of septic shock. J Crit Care. 2020 Feb;55:48-55. doi: 10.1016/j.jcrc.2019.10.005. Epub 2019 Oct 23. PMID: 31706118.

Much of the available data suggests a combination of low-dose vasopressin infusion with norepinephrine increases mean arterial pressures while sparing catecholamine use, reduces rates of arrhythmia and kidney injury, and reduces mortality. When considering that vasoplegia is due to vasopressin deficiency and high NO levels, vasopressin becomes ideal to increase serum levels and suppress NO production.

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Methylene Blue/Hydroxocobalamin are Prefered First Choice Treatments of Vasoplegia

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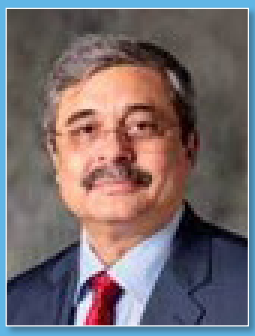

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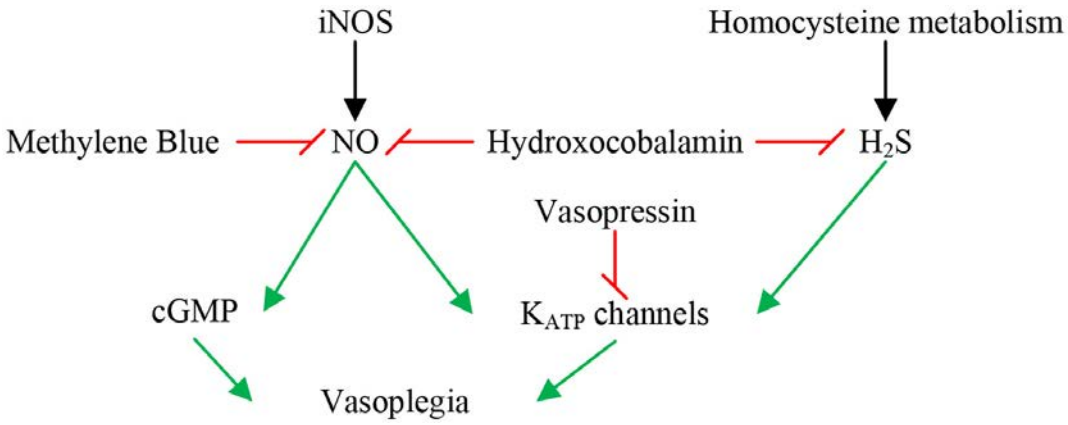
Vasoplegia is a type of vasodilatory or redistribution shock and occurs in up to 45% of cardiac surgical cases and may last for hours to days.[1,2,3,4] Although the definition varies, it includes a catecholamine-hyporesponsive hypotensive state with normal or elevated cardiac output and reduced systemic vascular resistance. Prolonged vasoplegia lasts > 6-8 hours and associated with end-organ hypoperfusion causing renal, liver, and pulmonary dysfunctions, and a metabolic acidosis.[1,2,3,5,6] Vasoplegia lasting > 36 hours prolongs mechanical ventilation, ICU and hospital stay, and mortality.[1,2,3,5,6] The inflammatory response to surgery, the cardiopulmonary bypass machine, and eventual reperfusion increases release of inflammatory cytokines which elevates Nitric Oxide Synthase (NOS) activity, increases Nitric Oxide (NO) production, and leads to the conversion of GTP to cGMP. NO and cGMP decrease calcium entry into the intracellular space, stimulates calcium sequestration into the sarcoplasmic reticulum to reduce vascular smooth muscle cell (VSMC) contraction.[4,7] In addition, KATP channels are kept open to create a hyperpolarized hyporesponsive cell membrane.[4] These are the major drivers of vascular/redistribution shock, vasoplegia and vascular smooth muscle cell (VSMC) hypo-responsiveness.[4,7] Hydrogen Sulfide (H2S) is normally cardioprotective and reduces stabilizes endothelium and prevents cellular apoptosis.[8] At high concentrations, seen in inflammatory states, H2S directly activates and hyperpolarizes KATP channels, therefore reducing the vascular tone and responsiveness, a state like that seen with NO.[8,9,10,11,12] H2S also inhibits phosphodiesterase and increasing cGMP and NO (8,10,11,12). These pathways act synergistically.[3]



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Methylene Blue

Methylene Blue depresses NOS activity, scavenges, and reduces NO levels, and inhibits cGMP.[13] Methylene Blue administration increases blood pressure and reduces catecholamine needs in patients with vasoplegia due to sepsis and vasoplegia associated with cardiac surgery.[14] Dosing of Methylene Blue varies across the literature from 1-3 mg/kg single shot administration with or without repeat doses. The half-life is 5-6.5 hours and excreted in the urine within 24 hours. Repeat doses may be given every six hours or, alternatively, an infusion can be initiated; 250-500mg/hr or 0.25-0.50 mg/kg/hr.

Adverse effects of Methylene Blue are uncommon but include coronary, mammary, and

splanchnic artery constriction, serotonin syndrome and hemolysis, the latter is those with G6PD deficiency.[1] A green urine discoloration occurs. There is a transient interference with the pulse oximeter analysis of oxygen saturation.

In 88 refractory vasoplegia cases, Methylene Blue increased systemic pressure and reduced the doses of catecholamine medications.[15] The benefits of MetBlue have been described in cardiac surgical patients, patients with liver dysfunction, or in the presence of sepsis.[16] In addition to improving systemic blood pressure, Methylene Blue may also increase cardiac performance and reduce spinal cord injury.[17,18]

In a review of 118 high risk patients the administration of Methylene Blue reduced norepinephrine use and reduced lactate levels.[19] Those who received it early (operating room vs intensive care unit) had a lower adverse event rate and reduced operative mortality (10.4% vs 28.5%; p = 0.0018).[19] In a retrospective 10-year review of 1022 patients with post cardiac surgery vasoplegia (hypotension despite norepinephrine > 0.3 ug/kg/min and vasopressin >0.1U/min), 221 received Methylene Blue (2mg/kg) during surgery, 60 of which received it within 15 minutes of diagnosis.[20] Earlier administration had a greater increase in mean arterial pressure (MAP) and more significant reduction in norepinephrine and vasopressin during over two hours. The Methylene Blue group received significantly less fluid and fresh frozen plasma.[20] Similarly, for septic patients those who received Methylene Blue early have better survival.[21,22] In an analysis of 6 articles with 214 vasoplegic patients, compared to a control group Methylene Blue significant increased MAP and reduced serum lactate levels, with a trend toward lower mortality.[23]

Prophylactic administered of 1.5-2 mg/kg Methylene Blue has benefits over placebo.[24,25,26] For patients with jaundice undergoing related surgery, prophylactic Methylene Blue resulted in greater hemodynamically stability with fewer requiring norepinephrine to sustain a MAP > 65mmHg.[24] Of those that did receive norepinephrine, the total dose was lower in the Methylene Blue group.[24] Finally, those receiving Methylene Blue recorded lower serum creatinine, less acute kidney injury, and lower liver enzymes over the three postoperative days.[24] In a randomized study of patients receiving ACEi scheduled for cardiac surgery, the prophylactic Methylene Blue (3 mg/kg) given at the onset of cardiopulmonary bypass, was associated with greater hemodynamic stability, less intravenous vasopressor administration, and lower serum lactate levels.[25] In a randomized study, cardiac patients who received Methylene Blue (2mg/kg) infusion over 6 hours recorded higher post cardiopulmonary bypass blood pressure and systemic vascular resistance for 3 and 6 hours respectively.[26] TNF- and NO levels were lower in the Methylene Blue group for 24 hours.[26]

Dosing of Methylene Blue varies from single administration to continuous infusions or a combination of the two. In 209 ICU patients with vasoplegia and shock defined by the administration of norepinephrine > 0.1 ug/kg/min and a serum lactate > 2 mmol/L (27). Three dosing strategies of Methylene Blue were compared. Methylene blue was administered if a norepinephrine dose >0.3 µg/kg/min and vasopressin of 0.06 IU/kg/min could not increase MAP > 65 mmHg (27). Dosing regimens of Methylene Blue included a bolus (2mg/kg) without an infusion, a bolus (2mg/kg) with an infusion (0.25 mg/kg/hr), and an infusion only (0.25mg/kg/hr). Response to Methylene Blue was 59% overall, with the two bolus groups being 60-64% and the infusion only group being 45%.[27] Although the use of vasoactive medications declined in all three groups, the 28-day mortality was significantly low in the bolus/infusion group (53% vs > 70%).[27] 91 patients with septic shock and vasoplegia requiring norepinephrine diagnosed within 24 hours and who had an elevated lactate (> 2 mmol/L) were randomized to receive Methylene Blue (n=45) and placebo (n=46).[28] 100 mg of Methylene Blue was administered over 6 hours each day for three days and compared to an equivalent dose of saline. The Methylene Blue group received less norepinephrine and for a shorter period, received less fluid, and had shorter ICU and hospital stay.[28]

Although improved hemodynamics with Methylene Blue are consistent, outcome data vary. In a randomized study of 56 patients with vasoplegia, 28 received 1.5 mg/kg of Methylene

Blue.[5] Vasoplegia duration was less in the Methylene Blue group, lasting less than 3 hours for all, compared to placebo from which 8 patients experienced vasoplegia longer than 48 hours .[5] The Methylene Blue had less morbidity and mortality (0% vs 21.4%) than those receiving placebo.[5] A meta-analysis of 15 studies and 832 patients from various clinical scenarios with vasodilatory shock concluded that co-administration of Methylene Blue (1-2 mg/kg +/- infusion) improved hemodynamics, reduced vasopressor use, reduced lactate levels, and improved survival.[29] In a retrospective analysis, 28 post-cardiac surgical patients with vasoplegia who received Methylene Blue (2mg/kg +/- 0.5-1.0 mg/kg/hr) were matched with historical controls who were managed conventionally for their vasoplegia.[30] Vasoplegia resolved sooner (8 vs 30 hours) and the time for discontinuing vasoactive medications was shorter (23 vs 55 hours) in the Methylene Blue group.[30] ICU (7 vs 12 days) and Hospital (11 vs 20 days) length of stays were shorter, there was less renal failure (7 vs 32%) and a lower mortality (3.6 vs 21%) in the Methylene Blue group.[30]

Considering the central and major role that NO has in initiating and sustaining vasoplegia, administration of Methylene Blue is logical. Considering the benefits, early administration, perhaps an initial administration followed by either repeat doses or an infusion may improve responsiveness and sustained benefit.[31]

Hydroxocobalamin (Cyanokit)

The inflammation triggered by infection, surgical trauma, and cardiopulmonary bypass increase NOS activity, NO production, and causes endothelial dysfunction and vascular inflammation promoting the production of hydrogen sulfide (H2S). Although H2S typically protects cells from oxidative stress and ischemia-reperfusion injury, an excess result in vasodilation due to opening of KATP channels causing transmembrane hyperpolarization and hypo-responsiveness, and possible a reduction of angiotensin II formation by type I angiotensin-converting enzyme (ACE 1).[9,32,33]

Hydroxocobalamin inhibits NOS enzymes[34], directly inactivates, and scavenges NO[35] and reduces H2S levels and toxicity through direct binding.[1,36,37,38,39,40] Hydroxocobalamin increases the effects of vasopressors on the KATP channel increasing responsiveness, may improve cardiac contractility (36) and has very few side effects.[10,34,41,42] Side effects of Hydroxocobalamin include urine discoloration (dark orange/red) erythema, rash, headache, and rare photosensitivity and renal failure.[10] There is a transient interference with the pulse oximeter.

Hydroxocobalamin has applied for the treatment of refractory vasoplegia after CPB, using the same protocol of administration as in cyanide poisoning (5 g administered by IV infusion over 15 min). Several case reports and case series recorded increased MAP and reduction in vasopressors with administration of Hydroxycobalamin.[10,42,43] In a retrospective study of 33 patients treated with hydroxocobalamin for refractory hypotension during or after CPB, a pressor effect was noted in 24 patients.[44.]

While less researched than Methylene Blue for managing vasoplegia, case reports and small series demonstrate the benefits of hydroxocobalamin in high-risk patients already receiving combinations of high doses of Norepinephrine (> 0.1 ug/kg/min), Epinephrine (> 0.1 ug/kg/min) and/or Vasopressin (> 0.04U/min).[32,42,45,46] Other case reports describe hydroxocobalamin rescue after resistance or refractoriness to methylene blue consistent with a non-NO mechanism.[45,47]

Dosing ranges from 5 grams to 10 grams administered intravenously over 10-15 minutes with one report describing a continuous infusion of 250-500 mg/hr.[32,46,48] Like other acute therapies for vasoplegia, the response rate varies for Hydroxocobalamin being approximately 70-75% and variable duration of benefit.[40,42,44]

While there is no randomized trial reporting its benefits, the multiple rescue cases and case series support its use for refractory vasoplegia. Additionally, in experimental conditions the use of Hydroxocobalamin improved survival of test animals exposed to H2S.[36] In a double

blind randomized controlled trial, Hydroxocobalamin improved hemodynamics by > 10%, reduced vasopressor needs between 23-28%, and reduced H2S levels.[42,49]

For the refractory hemodynamic state, it is logical to target the mechanism of vasoplegia. Methylene Blue and Hydroxocobalamin inhibit NOS, binds, scavenges, and prevents production of NO and H2S (REFERENCES). By reducing excess NO and H2S, Methylene Blue and Hydroxycobalamin increase MAP while reducing lactate levels.[25,50] By contrast Vasopressin and Angiotensin increase intracellular calcium and are associated with digital, mesenteric, and/or cardiac ischemia (REFERENCES). Vasopressin and Angiotensin vary in responsiveness to as low as 50-60%, and efficacy does not correlate with serum levels, the latter reported as equal for both responders and non-responders.[51,52,53,54] Reduced efficacy of vasopressors may be related to a downregulation of receptors by cytokines and NO.[55] While varied response rates may reflect the severity of disease and dysfunction, it also suggests a refractory state not overcome with increasing intracellular calcium.[56] However, addressing the central mechanisms/pathways causing vasoplegia, such as NO, and H2S may overcome this and improve the response to more pure vasoconstrictors.[57,58] When Methylene Blue alone is compared to combined therapy with Hydroxycobalamin, an advantage, i.e., increased MAP, was seen within an hour.[58]

Membrane hyperpolarization reduced intracellular calcium, and endoplasmic reticulum sequestration of calcium are the result of excess NO and H2S. Vasodilation and hypo-responsiveness are the result and defines vasodilation. First line therapy should counter the effects of NO and H2S to improve hemodynamics, end-organ perfusion, and outcome. Even if vasopressors are still necessary, at least the dose will be reduced and their effects more significant.

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