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Impact of Vascular Aging in Patients Presenting with Hypertension, Coronary Artery Disease or Heart Failure and Cardiogenic Shock

Lawrence J Mulligan[1,2*], Christopher Potestio[1,2], Kenyon Sprankle[2]

[1]*Department of Anesthesiology, Cooper University Hospital, Camden, NJ, USA*
[2]*Cooper Medical School of Rowan University, Camden, NJ, USA*

ABSTRACT

Cardiogenic Shock (CS) presents a complex physiological environment for physicians to navigate. The presence of CS is frequently found in patients suffering from Hypertension (HTN), Coronary Artery Disease (CAD) and Heart Failure (HF). Adding to these disease states is the underlying and underappreciated state of Vascular Aging (VA) and subsequent microvascular dysfunction. Vascular aging includes the loss of aortic compliance and is logically associated with the disease states listed and is quantified using pulse-wave velocity and an increase in the Augmentation Index (AIx).

These disease states are also associated with a loss of microvascular regulation of blood flow. The loss of aortic compliance coupled with microvascular dysfunction presents a complicated setting for the intensive care physician. Restoration of perfusion pressure is the goal, but the presence of vascular aging combined with cardiovascular diseases impacts the success rate in the CS patient. Understanding how the presence of VA coupled with microvascular dysfunction may add to the complexity of treatment is the focus of this review.

Keywords: Cardiogenic shock; Hypertension; Dysfunction; Augmentation index; Coronary artery disease

INTRODUCTION

Underappreciated for decades, Laurent et al and other have provided insight into the concept of Vascular Aging (VA) and how the presence of VA impacts cardiovascular function [1-8]. The loss in macro-vascular function due to age is different from the pathophysiological changes in the micro-vascular bed [9,10].

The loss of the functional and structural properties of the large "conduit" arteries has been examined in depth. While the aging process is associated with an increase in aortic diameter and stiffness, a loss in endothelial function and an increase in intima thickness also occur [11-14]. The micro-vascular bed undergoes a loss in vascular tone and permeability [14]. The important link to focus on in the macro and microvascular relationship is that the aging and disease process impacts each bed differently but leads to a synergistic loss in overall hemodynamic stability.

The loss of Aortic Compliance (C_A) occurs with age, free of disease, with four notable findings. First, the aortic diameter increases. Second, the change in diameter during the cardiac cycle is decreased. Third, the pulse wave velocity increases and finally, the size and amount of reflected wave arriving in systole increases. During the aging process, systolic blood pressure or central aortic blood pressure and pulse pressure will rise. During this process, the loss in C_A is coupled with a loss in small muscular artery compliance (<2 mm).

The loss in the functional regulation of the resistance bed, with age and/or disease (lumen diameter <350 µm) accounts for 45%-50% of peripheral resistance, this leads to an overall increase in systolic pressure and cardiac work. In the healthy macro and micro vasculatures, a balance between cardiac work with organ perfusion is tightly controlled. A loss in this relationship,

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Corresponding author Lawrence J Mulligan, Department of Anesthesiology, Cooper University Hospital, Camden, NJ, USA, E-mail: mulligan-lawrence@cooperhealth.edu

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due to an increase in conduit and muscular arteries leads to an increase in cardiac work and a loss of autoregulation in organ beds. The consequences of cardiovascular disease (HTN, CAD and/or heart failure) lead to a greater loss of the function of this macro-micro relationship.

In the patients presenting with CS coupled with the various disease states listed, manipulation of systemic vascular resistance to maintain a physiologic Mean Arterial Pressure (MAP) and Cardiac Output (CO) may be impaired [9,10,14,15]. Depending on the vascular age of the patient, the ability to control MAP and CO during CS will be impacted and is likely to create a more complicated treatment plan for the physician.

This review will provide an overview of how the loss in the function of the macro and micro vascular bed impacts the care of the patient presenting with CS.

LITERATURE REVIEW

Vascular Aging

Advanced age (especially >70 years) is one of the most significant adverse prognostic indicators in patients with CS, contributing to poorer outcomes and higher mortality rates [16]. Known microvascular impacts of VA include decreased vasodilation and increased endothelium-dependent contraction. This decrease in vascular responsiveness plays a large role in the impaired ability for the body to be able to respond to the hemodynamic mayhem introduced in a patient undergoing CS. The mechanism responsible for this decrease in vascular responsiveness is that the leukocyte endothelia contribute to vascular inflammation leading to increased adhesion and activation of platelets, a known risk factor for exacerbation of cardiovascular disease. Impairment of endothelium induced vasodilation, enhanced vasoconstriction, and increased production of reactive oxygen species leads to inflammation of the vascular wall impacting the microvasculature [17, 18].

Vascular aging can occur separately from or in association with other important cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, and obesity. These conditions may further accelerate the underlying mechanisms that lead to vascular aging. Due to the complex and interwoven ways in which many of these additional conditions impact the micro and macro vascular circuits it is important to handle treatment decisions for individuals undergoing CS on a case-by-case basis as opposed to managing patients primarily by perceived vascular age [19].

Hypertension (HTN)

Hypertension (HTN) is defined as systolic blood pressure >130 mmHg and/or diastolic blood pressure >80 mmHg and when chronic can result in a multitude of macro vascular and microvascular changes collectively known as vascular senescence at the cellular level [20]. As described by Laurent et al. the first stage includes small artery damage with vasoconstriction, impaired vasodilation, increased media-lumen ratio and a reduced lumen diameter resulting in an elevation in peripheral resistance [21]. The second stage involves the consequence of the first step leading to large increases in blood pressure and an increase in large artery stiffness. These two steps create a synergetic impact and lead to increases in central systolic and pulse pressure and the continued structural alterations in the small resistance vessels. This leads to an increase in wave reflections, elevated central systolic, pulse pressures and an increase in Pulse Wave Velocity (PWV) [21]. The result is an increase in central aortic blood pressure and PWV with continued damage to the small resistance arteries. These steps combine to structurally change the small resistance vessels that govern 40%-50% of peripheral resistance.

Hypertension is a significant risk factor for the development of Cardiogenic Shock (CS), particularly in patients with Acute Myocardial Infarction (AMI) [22]. Even in early stages of the disease, hypertension results in vascular remodeling which activates distinctive intracellular pathways, resulting in structural and functional alterations that eventually induce vascular stiffness, increased systolic blood pressure and may contribute to the progression of atherosclerosis in the large elastic and small muscular arteries [2,20]. These dysfunctional changes that occur in the resistance vessels in the periphery and the coronary microvascular bed create an additional burden for the treating physician. In the setting of CS, the loss in nitric oxide production by the endothelium compounds the functional loss and changes in vascular smooth regulation in tone. In the macro-circulatory system, hypertensive patients with CS often have worse outcomes due to the pre-CS chronic strain on the heart from prolonged elevated blood pressure, leading to increased morbidity and mortality.

The loss of microvascular function requires a unique balance with preventing vasoconstriction as regional auto regulatory control is impaired. In the CS setting, the renal bed is at risk of under-perfusion with the consequences of acute kidney injury being a possibility in addition to the damage caused by VA. The restoration of perfusion may become more difficult to control due the presence of VA on the macro and micro-circulatory system.

Coronary Artery Disease (CAD)

In 1985, Cannon and Epstein introduced the term 'Micro Vascular Angina' (MVA) for this patient population, in view of what appeared to be heightened sensitivity of the coronary microcirculation to vasoconstrictor stimuli associated with a limited microvascular vasodilator capacity [23]. Although there was an initial attempt to group all these patients into one category, it was soon realized that they represent a spectrum of vascular disease states. The microvascular dysfunction observed in MVA adds more complexity to the ischemic burden present in patients with coronary artery disease impacting the larger vessels.

Coronary artery disease is found in up to 80% of individuals of patients with CS and multivessel CAD is associated with a higher mortality rate in individuals that experience CS than in individuals without CAD [24]. CAD is associated with a loss in the regulation of blood flow in the coronary microvascular bed. This presence of this dysfunction is separate from the disease pathology of VA detailed above. The coronary arteries and microvascular bed are not subjected to an increase in pulsatility found in patients with HTN and CAD. The additional

workload placed on the heart by the development of HTN and or CAD is coupled with a loss in coronary diastolic pressure. The arrival of the reflected wave in systole due to VA creates a lower coronary diastolic pressure in tissue that is already at the risk of ischemia. Microvascular beds regulate flow versus pressure but when the bed is vasodilated under local control, flow needs are exhausted, and the loss of perfusion pressure is another limiting variable to preserve adequate flow.

The presence of disease in the peripheral small muscular arteries is similar to the development of disease in the coronary arteries. However, the loss of microvascular control in the peripheral arterioles is not similar to the loss that occurs in the coronary arterioles due to the presence of increased pulsatility.

Treatment for individuals with CS and CAD must be handled on a case-by-case basis and the impact of VA is an important variable that has not been part of the patient assessment. These metrics provide insights that are not part of the cardiac output and mean arterial pressure paradigm. The development of Cardiac Power Output (CPO) was shown to be a discriminator for who is recovering from CS but this metric does not provide any insight into the pathophysiology of VA and its influence on the management of CS [25].

DISCUSSION

Heart Failure (HF)

Heart failure has been shown to have a component of VA with the disease state. The disruption of peripheral vascular function added to the consequences of CS may lead to more difficult treatment paradigm for the treating physician. In addition, many cases of heart failure may lead to cardiogenic shock and is associated with the disruption of macro-microvascular circuit [26]. The association of the structural loss in the entire coronary bed presents treatment issues in patients developing CS. The burden of coronary stenosis coupling with a loss of microvascular regulation magnifies the treatment difficulty.

CONCLUSION

Taken in isolation, each of these disease states HTN, CAD, and HF lead to important microvascular changes in addition to the large vessel changes such as blood pressure that we use to guide therapy. Many of the pathways of inflammation, damage to vessels, and lack of physiologic responsiveness to nitrous oxide and other agents are similar among the disease states. They also have a large degree of overlap with physiologic changes of VA. While the clinical focus should be tailored to each patient's unique combination of these disease states, future research on CS should focus on better understanding and monitoring of a patient's microcirculation and vascular aging.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

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AUTHORS CONTRIBUTION

LJM: Conceptualization, Writing-original draft, Project Administration, Writing–Original Draft, Writing–Review and Editing.

KS: Data Curation, Writing-Review and Editing.

CP: Conceptualization, Writing-Writing-original draft.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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