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THE PATHOPHYSIOLOGY OF VASOPLEGIC SYNDROME FOLLOWING CARDIOPULMONARY BYPASS: ENDOTHELIAL DYSFUNCTION, THE NITRIC OXIDE PATHWAY AND THE INFLAMMATORY RESPONSE

Bişar AMAÇ, 0000-0003-0320-4239
Harran University, Faculty of Health Sciences, Department of Perfusion, Post code: 63290 Sanliurfa, Türkiye

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Correspondence: *Bişar Amaç, amacbisar@gmail.com*

ABSTRACT

Although cardiopulmonary bypass is a fundamental technique in cardiac surgery that enables the maintenance of systemic circulation and oxygenation, it creates an environment that differs significantly from physiological circulatory conditions. Contact of the blood with artificial surfaces, haemodilution, non-pulsatile flow, ischaemia-reperfusion processes and the systemic inflammatory response can lead to various haemodynamic and cellular abnormalities following cardiopulmonary bypass. One such disorder, vasoplegic syndrome, is a serious clinical condition characterised by low systemic vascular resistance, refractory hypotension and, typically, preserved or increased cardiac output.

In current approaches, vasoplegia is regarded not merely as a haemodynamic problem, but as a multidimensional pathophysiological syndrome associated with endothelial dysfunction, excessive activation of the nitric oxide pathway, impaired vascular smooth muscle response, relative vasopressin deficiency, inflammatory cytokine release and microcirculatory dysfunction. In the development of the vasoplegic syndrome, inducible nitric oxide synthase activation, increased nitric oxide production, relaxation of vascular smooth muscle cells, unresponsiveness to catecholamines, and impaired perfusion at the capillary level are particularly prominent.

As a result, systemic arterial pressure decreases, the need for vasopressors increases, and tissue oxygenation may be compromised. This process is associated with clinical outcomes such as acute kidney injury, elevated lactate levels, prolonged intensive care unit stay, and multiple organ dysfunction. The aim of this mini-review is to comprehensively evaluate the pathophysiological basis of the vasoplegic syndrome developing after cardiopulmonary bypass, focusing on endothelial dysfunction, the nitric oxide pathway, the inflammatory response, biomarkers, and organ hypoperfusion.

Keywords: Cardiopulmonary bypass, vasoplegic syndrome, endothelial dysfunction, nitric oxide, inflammation, microcirculation, pathophysiology

KARDİYOPULMONER BYPASS SONRASI VASOPLEJİK SENDROMUN FİZYOPATOLOJİSİ: ENDOTEL DİSFONKSİYONU, NİTRİK OKSİT YOLU VE İNFLAMATUVAR YANIT

ÖZET

Kardiyopulmoner bypass, kardiyak cerrahide sistemik dolaşımın ve oksijenlenmenin sürdürülebilmesini sağlayan temel bir yöntem olmakla birlikte, fizyolojik dolaşım koşullarından önemli ölçüde farklı bir ortam oluşturur. Kanın yapay yüzeylerle teması, hemodilüsyon, non-pulsatil akım, iskemi-reperfüzyon süreçleri ve sistemik inflamatuvar yanıt, kardiyopulmoner bypass sonrası çeşitli hemodinamik ve hücresel bozukluklara yol açabilir. Bu bozukluklardan biri olan vasoplejik sendrom, düşük sistemik vasküler direnç, dirençli hipotansiyon ve genellikle korunmuş veya artmış kardiyak debi ile karakterize ciddi bir klinik tablodur.

Güncel yaklaşımlarda vasopleji, yalnızca hemodinamik bir sorun olarak değil; endotel disfonksiyonu, nitrik oksit yolunun aşırı aktivasyonu, vasküler düz kas yanıtının bozulması, göreceli vazopressin eksikliği, inflamatuvar sitokin salınımı ve mikrodolaşım bozukluğu ile ilişkili çok boyutlu bir fizyopatolojik sendrom olarak değerlendirilmektedir. Vasoplejik sendromun gelişiminde özellikle indüklenebilir nitrik oksit sentaz aktivasyonu, artmış nitrik oksit üretimi, vasküler düz kas hücrelerinde gevşeme, katekolaminlere yanıtsızlık ve kapiller düzeyde perfüzyon bozukluğu ön plana çıkmaktadır.

Bunun sonucunda sistemik arter basıncı düşmekte, vazopressör ihtiyacı artmakta ve doku oksijenlenmesi bozulabilmektedir. Bu süreç akut böbrek hasarı, laktat yüksekliği, yoğun bakım süresinde uzama ve çoklu organ disfonksiyonu gibi klinik sonuçlarla ilişkilendirilmektedir. Bu mini derlemenin amacı, kardiyopulmoner bypass sonrası gelişen vasoplejik sendromun fizyopatolojik temelini; endotel disfonksiyonu, nitrik oksit yolu, inflamatuvar yanıt, biyobelirteçler ve organ hipoperfüzyonu ekseninde bütüncül olarak değerlendirmektir.

Anahtar Kelimeler: Kardiyopulmoner bypass, vasoplejik sendrom, endotel disfonksiyonu, nitrik oksit, inflamasyon, mikrodolaşım, fizyopatoloji

1. INTRODUCTION

Cardiopulmonary bypass enables the safe management of the surgical site by temporarily taking over the functions of the heart and lungs during open-heart surgery. However, the artificial circulatory environment created during cardiopulmonary bypass differs from physiological circulation and can trigger numerous pathophysiological processes, such as a systemic inflammatory response, oxidative stress, endothelial activation, changes in coagulation, and microcirculatory dysfunction (1,2).

One of the significant haemodynamic complications observed following cardiopulmonary bypass is vasoplegic syndrome. Vasoplegia is generally characterised by low systemic vascular resistance, refractory hypotension and normal or increased cardiac output. Clinically, despite adequate intravascular volume and cardiac output, arterial pressure remains low in patients, and a requirement for high-dose vasopressors may arise (3,4).

The clinical significance of vasoplegic syndrome following cardiac surgery stems from its potential association with tissue hypoperfusion, elevated lactate levels, acute kidney injury, prolonged mechanical ventilation, extended intensive care unit stay, and increased mortality. Therefore, understanding the mechanisms of vasoplegic syndrome is important for both early diagnosis and the development of targeted treatment strategies (5).

2. CARDIOPULMONARY BYPASS AND THE SYSTEMIC INFLAMMATORY RESPONSE

During cardiopulmonary bypass, contact between the blood and the surfaces of the extracorporeal circuit leads to the activation of the immune system and the complement system. In this process, neutrophils, monocytes, platelets and endothelial cells are activated. Cytokine release, leukocyte adhesion, oxidative stress and increased vascular permeability constitute the key components of the systemic inflammatory response (1,6).

This inflammatory response may directly affect the mechanisms involved in the regulation of vascular tone. In particular, pro-inflammatory cytokines can increase nitric oxide production in endothelial cells, reduce the response of vascular smooth muscle cells to vasoconstrictor agents, and cause perfusion heterogeneity at the capillary level. Consequently, systemic vascular resistance decreases in the post-cardiopulmonary bypass period, and a vasoplegic syndrome may develop (3,7).

During this process, inflammation does not merely affect systemic arterial pressure; it can also disrupt the balance between oxygen supply and oxygen utilisation at the microcirculatory level. Even if macrohaemodynamic parameters remain within acceptable limits, tissue-level hypoxia may develop due to heterogeneity in capillary flow and impaired endothelial barrier integrity (2,8).

3. ENDOTHELIAL DYSFUNCTION AND LOSS OF VASCULAR TONE

The endothelium is an active structure that plays a central role in regulating vascular tone, maintaining coagulation balance, facilitating the migration of inflammatory cells, and preserving microcirculatory integrity. Inflammation, oxidative stress, haemodilution, ischaemia-reperfusion, and non-physiological flow characteristics that develop during cardiopulmonary bypass can impair endothelial function (2).

Endothelial dysfunction disrupts the balance between vasodilator and vasoconstrictor mediators. Under normal conditions, the endothelium regulates vascular tone via mediators such as nitric oxide, prostacyclin and endothelin. However, following cardiopulmonary bypass, when inflammatory activation occurs in endothelial cells, excessive nitric oxide production and vascular smooth muscle relaxation may become pronounced (3,7).

Endothelial dysfunction is also associated with increased capillary permeability. Disruption of the capillary barrier can increase the transfer of intravascular fluid into the interstitial space. This may reduce the effective circulating volume, increase the need for vasopressors, and adversely affect organ perfusion. Consequently, in vasoplegic syndrome, endothelial damage is one of the key determinants of both loss of vascular tone and microcirculatory impairment (2,8).

4. THE NITRIC OXIDE PATHWAY AND THE MECHANISM OF VASODILATION

One of the most significant pathophysiological mechanisms of vasoplegic syndrome is the excessive activation of the nitric oxide pathway. The inflammatory response that develops following cardiopulmonary bypass may increase the activation of inducible nitric oxide synthase. As a result, large amounts of nitric oxide are produced. Nitric oxide causes relaxation by activating the cyclic guanosine monophosphate pathway in vascular smooth muscle cells and reduces systemic vascular resistance (3,7).

At the physiological level, nitric oxide is essential for maintaining vascular tone and regulating microcirculation. However, excessive nitric oxide production can lead to pathological vasodilation and a lack of response to vasopressors. Consequently, in vasoplegic syndrome, nitric oxide plays a dual role: whilst it maintains vascular homeostasis at normal levels, at excessive levels it contributes to uncontrolled vasodilation and hypotension (7).

This mechanism may result in catecholamine resistance in the clinical setting. In patients, adequate arterial pressure may not be achieved despite the administration of noradrenaline or other vasopressors. This condition is associated not only with a lack of response at the receptor level, but also with a cellular-level disruption of vascular smooth muscle contraction mechanisms (4,9).

5. VASOPRESSIN DEFICIENCY AND CATECHOLAMINE RESISTANCE

In vasoplegic syndrome, not only an increase in nitric oxide but also a relative deficiency of vasopressin is considered a significant mechanism. Vasopressin induces vasoconstriction via V1 receptors on vascular smooth muscle and contributes to the maintenance of arterial pressure. Insufficient vasopressin response in the post-cardiopulmonary bypass period may lead to a further decrease in systemic vascular resistance (9,10).

Catecholamine resistance, however, is one of the key issues complicating the clinical management of vasoplegic syndrome. In such cases, an adequate vasoconstrictor response may not be achieved despite the use of high doses of catecholamines. Catecholamine resistance is associated with receptor desensitisation, acidosis, inflammatory mediators, excessive nitric oxide production and impaired vascular smooth muscle contractility (4,9).

For this reason, vasoplegic syndrome differs from classic presentations of hypotension. The problem is not merely a deficiency in intravascular volume or myocardial pump failure; the main issue is the pathological relaxation of the vascular bed and its inability to respond adequately to vasoconstrictor stimuli (3,4).

6. MICROCIRCULATORY DISORDER AND ORGAN HYPOPERFUSION

In vasoplegic syndrome, macrohaemodynamic findings may not always correlate with tissue-level perfusion. Even if cardiac output is preserved or increased, blood flow distribution at the microcirculatory level may be impaired. Capillary flow heterogeneity, endothelial barrier

damage, leukocyte-endothelial interaction and interstitial oedema can hinder the delivery of oxygen to the tissues (2,8).

This situation can lead to clinical consequences, particularly in organs sensitive to changes in perfusion, such as the kidneys, brain, myocardium and gastrointestinal system. Acute kidney injury, elevated lactate levels, prolonged intensive care unit stay and multiple organ dysfunction are significant manifestations of this process (5,11).

Therefore, when assessing vasoplegic syndrome, it is not only arterial pressure and the need for vasopressors that should be considered; lactate, urine output, creatinine, venous oxygen saturation, base deficit and indicators of organ function must also be taken into account (5,11).

7. BIOMARKERS IN VASOPLEGIC SYNDROME

In recent years, there has been growing interest in biomarkers for the early diagnosis and risk stratification of vasoplegic syndrome. However, there is still no single, standard and widely accepted biomarker that can diagnose vasoplegia on its own. Current studies are investigating the association between markers related to inflammation, endothelial activation, vascular tone and metabolic stress and vasoplegic syndrome (12).

Biomarkers that may be evaluated in the context of cardiac surgery and cardiopulmonary bypass include IL-6, TNF-α, IL-10, procalcitonin, C-reactive protein, lactate, nitric oxide metabolites, markers of endothelial damage, and molecules associated with glycocalyx damage. These biomarkers may help in understanding the inflammatory, endothelial and microcirculatory components of vasoplegia (2,12).

However, for biomarkers to be introduced into clinical practice, their relationship with timing, threshold values, patient groups, surgical procedures and treatment response needs to be defined more clearly. In particular, it should be investigated whether biomarkers have not only diagnostic but also prognostic value in the post-cardiopulmonary bypass period (12).

8. CLINICAL MANIFESTATIONS

The clinical presentation of vasoplegic syndrome following cardiopulmonary bypass typically manifests as low systemic vascular resistance, refractory hypotension and an increased need for vasopressors. Cardiac output may be normal or elevated. In this respect, vasoplegia must be distinguished from low cardiac output syndrome (3,4).

This distinction is clinically important. This is because, in a vasoplegic patient, fluid loading or inotropic support alone may not be sufficient. Excessive fluid administration may increase interstitial oedema and adversely affect organ function. Therefore, haemodynamic assessment should be carried out by considering cardiac output, systemic vascular resistance, filling pressures, lactate, urine output and organ function together (5,11).

In severe forms of vasoplegic syndrome, there may be a need for high doses of vasopressors, elevated lactate levels and organ dysfunction may develop. Therefore, early diagnosis, the identification of high-risk patients and the planning of treatment strategies based on the pathophysiology are important (11,12).

9. CONCLUSION

Vasoplegic syndrome following cardiopulmonary bypass is not merely a simple haemodynamic disorder limited to postoperative hypotension. This condition is a complex pathophysiological syndrome in which a systemic inflammatory response, endothelial dysfunction, excessive activation of the nitric oxide pathway, impaired vascular smooth muscle contractility, relative vasopressin deficiency, catecholamine resistance and microcirculatory dysfunction all play a role.

Understanding the pathophysiology of vasoplegic syndrome may provide significant clinical insights into patient management following cardiac surgery. In particular, the combined assessment of CPB duration, inflammatory response, lactate levels, renal function, vasopressor requirements and biomarkers may aid in the early identification of high-risk patients.

In conclusion, vasoplegic syndrome following cardiopulmonary bypass is an important, current and research-worthy topic from the perspectives of perfusion pathophysiology, cardiovascular surgery and intensive care practice. Therefore, this topic provides a strong academic foundation for both a mini-review and for prospective or retrospective clinical research in the future.

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