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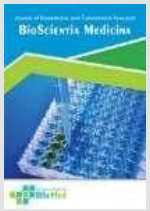

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The Eye as a Window to Systemic Hemodynamics: A Novel Approach to Estimating Central Venous Pressure via Tonometry in Sepsis

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A B S T R A C T

Background: Effective hemodynamic management in sepsis is critical, yet current practices are constrained by the risks and interpretive challenges of invasive central venous pressure (CVP) monitoring. The clinical utility of CVP is debated, fueling the search for safer alternatives. This study investigates a novel approach, exploring intraocular pressure (IOP) as a non-invasive surrogate for CVP, predicated on the direct anatomical link between the ocular venous drainage system and the central circulation. **Methods:** We conducted a prospective, single-center observational study in a tertiary intensive care unit, enrolling 20 adult patients with sepsis and indwelling central venous catheters. High-fidelity measurements of CVP via a pressure transducer and IOP via Perkins applanation tonometry were performed simultaneously. Data were collected at a baseline steady-state and again 15 minutes after a standardized fluid challenge (median volume 300 mL) to assess the dynamic relationship. The association was quantified using Pearson correlation and modeled with simple linear regression. **Results:** A strong, statistically significant positive correlation was observed between CVP and IOP at baseline ($r=0.756$, $p=0.001$). This physiological coherence was profoundly amplified following the fluid challenge, strengthening to a very strong correlation ($r=0.947$, $p<0.001$). The post-challenge data yielded a robust, preliminary predictive model, defined by the equation: CVP (mmHg) = -0.619 + (0.522 x IOP (mmHg)). The slope of this relationship was precisely estimated (95% CI: 0.435 to 0.609). The model demonstrated high predictive power, with post-challenge IOP accounting for 89% of the variance in CVP ($R^2=0.89$). **Conclusion:** This pilot investigation provides compelling evidence for a strong and dynamic correlation between IOP and CVP in critically ill patients with sepsis. The findings suggest that ocular tonometry shows significant promise as a non-invasive method for assessing right-sided filling pressures and, more importantly, for tracking the dynamic response to fluid therapy, thereby offering a potential window into venous congestion. While intriguing, these results are from a small cohort. The derived formula is strictly hypothesis-generating and requires extensive validation in larger, more diverse clinical trials before any potential for clinical application can be considered.

1. Introduction

Sepsis, a syndrome of life-threatening organ dysfunction arising from a dysregulated host response to infection, stands as a preeminent challenge in global health and a principal driver of mortality in intensive care units (ICUs).[1] The profound pathophysiology of sepsis is marked by a maelstrom of inflammatory mediators, leading to systemic vasodilation, endothelial barrier disruption, and a state of profound circulatory derangement.[2] Effective

management hinges on navigating a narrow therapeutic window: restoring adequate tissue perfusion through intravenous fluids and vasoactive agents, while simultaneously avoiding the iatrogenic harm of fluid overload, which precipitates organ edema, venous congestion, and increased mortality. This delicate balancing act demands accurate, real-time hemodynamic assessment. For decades, the measurement of central venous pressure (CVP) has been a cornerstone of this assessment. Obtained via an invasive central venous catheter (CVC), CVP reflects the pressure in the vena cava near the right atrium and has been traditionally employed as a proxy for right ventricular preload to guide fluid administration.[3] However, this practice is now steeped in controversy. A substantial body of evidence has demonstrated that a static CVP value is a poor predictor of fluid responsiveness—the capacity of the heart to augment its stroke volume in response to a fluid bolus.[4] Consequently, the role of CVP has evolved from a direct guide for fluid administration to a parameter more indicative of the upper limits of fluid tolerance and a marker of right ventricular function and systemic venous congestion.[5] Despite its limitations, CVP remains a source of valuable physiological information, but its acquisition comes at the cost of significant risks, including mechanical complications like pneumothorax, arterial puncture, and life-threatening hemorrhage, as well as infectious complications such as catheter-related bloodstream infections.[6]

These dual challenges—the invasive nature of the measurement and the nuanced interpretation of the data—have galvanized a search for safer, more accessible, and physiologically informative hemodynamic monitoring tools.[7] This study explores a conceptually elegant and anatomically plausible hypothesis: that the eye can serve as a non-invasive "window" to the central circulation. The intraocular pressure (IOP), the pressure within the anterior chamber of the eye, is governed by a delicate balance between aqueous humor production and its drainage.[8] The primary drainage pathway for this fluid is through the trabecular meshwork into a venous network that ultimately empties into the internal jugular vein via the valveless ophthalmic venous system.[9] This continuous, valveless fluid column provides a direct hydrostatic link between the central venous compartment and the eye. It is therefore physiologically coherent to posit that an elevation in downstream pressure (CVP) will impede aqueous humor outflow, thereby causing a corresponding rise in IOP. While preliminary research in non-septic populations, such as those undergoing cardiac or laparoscopic surgery, has shown a positive correlation, the relationship has never been rigorously tested in the unique and chaotic milieu of sepsis. Sepsis is not merely a state of hypovolemia; it is a syndrome of profound vasoplegia, endothelial injury, and altered microvascular permeability—factors that could fundamentally alter the transmission of pressure between the central and ocular circulations.[10]

The novelty of the present study resides in its dedicated and focused investigation of the CVP-IOP relationship specifically within a cohort of critically ill sepsis patients, a population where this link has not been rigorously established. We advanced beyond previous work by employing a high-precision, portable applanation tonometer (Perkins tonometer), representing the clinical standard for accuracy, to ensure the reliability of IOP measurements. Critically, the innovation of our study protocol incorporated a dynamic assessment, measuring the variables both at a baseline state and immediately after a standardized fluid challenge. This dynamic approach was designed to unmask a more robust and fundamental physiological correlation by assessing the system's response to a defined hemodynamic perturbation, rather than relying on a single, potentially misleading static measurement. The primary aim of this research was therefore twofold: first, to determine the strength, direction, and statistical significance of the correlation between CVP and IOP in sepsis patients, both at rest and under conditions of acute volume expansion. Second, based on these findings, we sought to derive

a preliminary, hypothesis-generating mathematical model to explore the potential for estimating CVP from a non-invasive IOP measurement, while critically appraising the physiological and clinical context in which such a tool might be used.

2. Methods

A prospective, single-center, observational correlational study was conducted in the adult ICU of Arifin Achmad Regional General Hospital in Riau, Indonesia, a tertiary care academic medical center. The study was designed to investigate the physiological relationship between two continuous variables, CVP and IOP, under baseline and dynamic conditions. The research protocol was executed in strict adherence to the tenets of the Declaration of Helsinki and received full approval from the Health and Medical Research Ethics Committee of the Faculty of Medicine, Universitas Riau (Approval No. 005/UN19.5.1.1.8/UEPKK/2025). Prior to any study-related procedures, written informed consent was obtained from the legally authorized representative of each enrolled patient. The target population included all adult patients (≥18 years) admitted to the ICU with a diagnosis of sepsis as defined by the Third International Consensus Definitions (Sepsis-3). We employed a consecutive sampling strategy, enrolling all eligible patients during the study period to minimize selection bias.

Inclusion criteria: Age ≥ 18 years; Confirmed diagnosis of sepsis or septic shock; Presence of an indwelling multi-lumen CVC (internal jugular or subclavian vein) as part of standard clinical care. Exclusion criteria: Refusal of informed consent; Known history of glaucoma, ocular hypertension, or other significant ocular pathology; Deep sedation or coma precluding cooperation; Use of mechanical ventilation with a Positive End-Expiratory Pressure (PEEP) level exceeding 5 cmH_2O.

The sample size was determined a priori to ensure adequate statistical power for a correlational analysis. Based on prior literature reporting a correlation coefficient (r) of approximately 0.66, with a type I error rate (α) of 0.05 and a desired power (1-β) of 0.90, the minimum required sample size was calculated to be 17 participants. To mitigate against potential data loss or patient withdrawal, the target sample size was increased by approximately 20% to a final cohort of 20 patients. Upon enrollment, we collected baseline demographic and clinical data, including age, sex, primary infection source, comorbidities, and the Sequential Organ Failure Assessment (SOFA) score. To ensure measurement consistency, all procedures were performed by a single, trained investigator. Measurement Protocol: 1. Baseline Measurement (Minute 0): Patients were positioned supine with the head of the bed elevated to 30-45 degrees. The CVP transducer was zeroed and leveled at the phlebostatic axis (fourth intercostal space, mid-axillary line). The CVP value (in mmHg) was recorded from the bedside monitor at end-expiration to minimize the influence of respiratory pressure swings. Immediately thereafter, one drop of topical pantocaine 2% was administered to one eye for anesthesia. IOP (in mmHg) was then measured in the anesthetized eye using a handheld, calibrated Perkins applanation tonometer. The final IOP value was recorded as the average of three consecutive readings. 2. Fluid Challenge: A fluid challenge was administered according to the treating clinician's judgment, consisting of an infusion of a balanced crystalloid solution. The volume administered ranged from 250-500 mL over 10-15 minutes. The median volume administered to the cohort was 300 mL. 3. Post-Challenge Measurement (Minute 15): Fifteen minutes following the completion of the fluid infusion, both CVP and IOP were re-measured using the identical techniques and patient positioning as the baseline assessment.

The dependent variable was CVP (mmHg) and the independent variable was IOP (mmHg). Data were analyzed using standard statistical software. Normality was assessed with the Shapiro-Wilk test. Pearson's correlation coefficient (r) was used to quantify the linear association between CVP and IOP, both before and after the fluid challenge. Simple linear regression analysis was performed to model the

relationship, generating a predictive equation ($Y = a + bX$). The coefficient of determination (R^2) was calculated to assess the model's explanatory power. The assumptions of linear regression were verified by visual inspection of residual plots. A p-value < 0.05 was considered statistically significant.

3. Results

Twenty patients with sepsis were enrolled and completed the study protocol. The cohort's demographic and clinical profile is detailed in Figure 1. Figure 1 provides a detailed and multi-faceted summary of the baseline demographic and clinical characteristics of the 20 critically ill patients with sepsis enrolled in this investigation. This figure serves as a crucial foundation, offering a clear and concise portrait of the population from which the study's primary physiological data were derived. The figure systematically presents key variables, allowing for a comprehensive understanding of the cohort's composition, severity of illness, and underlying clinical context. The demographic profile reveals a cohort with a median age of 46 years, yet encompassing a broad age spectrum that ranges from 23 to 87 years. This wide distribution suggests that the findings are not confined to a specific age bracket but represent a diverse adult population susceptible to sepsis. Furthermore, a significant gender imbalance is evident, with a notable male predominance; 70% of the participants were male, compared to 30% female. This distribution reflects a frequently observed epidemiological trend in sepsis and septic shock, highlighting the potential relevance of sex-based differences in host immune responses. Clinically, the figure underscores the profound severity of illness within the study group. The median Sequential Organ Failure Assessment (SOFA) score was 7, with an interquartile range indicating that the majority of patients presented with significant, life-threatening organ dysfunction. This confirms that the study population was representative of a typical cohort managed in a tertiary intensive care unit. The primary sources of infection leading to sepsis are also delineated, with the respiratory tract being the predominant origin in 50% of cases. This is followed by digestive sources (25%), bone and soft tissue infections (20%), and the urinary tract (5%), painting a clear picture of the infectious etiologies driving the septic process. Finally, the figure sheds light on the cohort's underlying vulnerability and the intensity of required medical intervention. A substantial burden of pre-existing comorbidities was present, with 30% of patients having a history of renal or hypertensive disease and 25% having cerebrovascular disease. This complex comorbidity profile is compounded by the high acuity of their septic state, evidenced by the fact that 75% of the cohort required vasopressor support to maintain adequate blood pressure. In synthesis, Figure 1 effectively portrays a clinically complex and highly relevant patient population, setting a robust and well-defined stage for the interpretation of the study's core hemodynamic findings.

The core study measurements are summarized in Figure 2. Figure 2 graphically illustrates the dynamic changes observed in central venous pressure (CVP) and intraocular pressure (IOP) in response to a standardized fluid challenge, providing a clear visual representation of the descriptive statistics for both parameters. In the left panel, depicting central venous pressure, the baseline mean CVP is shown to be 5.8 mmHg. Following the fluid challenge, the mean CVP significantly increased to 7.5 mmHg. This represents an average absolute increase of 1.7 mmHg (indicated by the "+1.7" arrow), demonstrating the expected physiological response of the central venous system to volume expansion. The standard deviation (SD) for CVP before the challenge was ±1.82 mmHg, and after the challenge, it was ±1.91 mmHg, indicating a consistent, albeit slightly increased, spread of data around the mean. The visual presentation uses a lighter blue bar for the "Before" state and a darker, more saturated blue for the "After" state, effectively conveying the change.

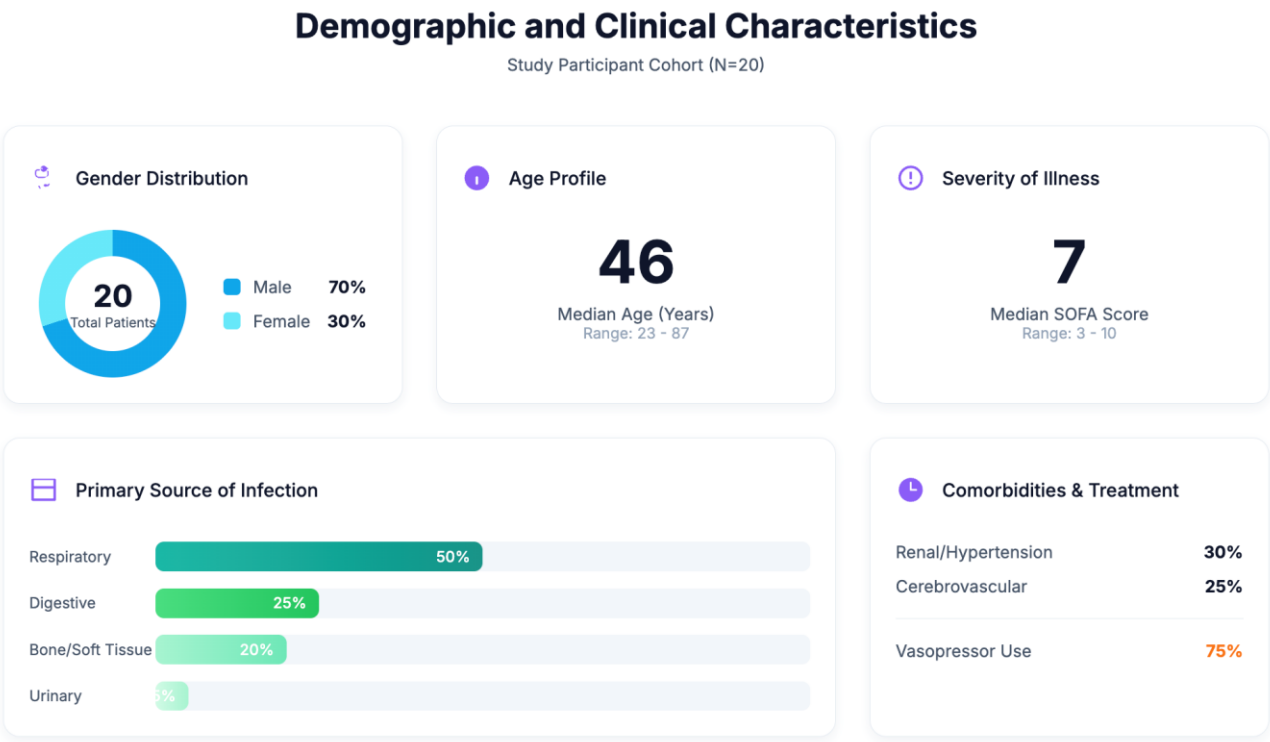

Figure 1. Demographic and clinical characteristics of study participants.

The right panel, illustrating Intraocular Pressure, presents a parallel pattern. The mean IOP measured at baseline was 13.0 mmHg. Post-fluid challenge, the mean IOP rose to 15.5 mmHg, marking an average absolute increase of 2.5 mmHg (indicated by the "+2.5" arrow). The standard deviation for IOP was ±2.41 mmHg before the challenge and ±3.46 mmHg after, suggesting a slightly greater variability in IOP response compared to CVP, potentially reflecting individual ocular biomechanical properties or responses to fluid shifts. A similar color scheme, utilizing a lighter green for the "Before" state and a darker green for the "After" state, maintains visual consistency with the CVP panel and clearly accentuates the observed increase. Figure 2 vividly demonstrates a congruent and quantitatively significant increase in both CVP and IOP following a fluid challenge in sepsis patients. The simultaneous elevation of these pressures provides initial visual evidence supporting the hypothesis that IOP mirrors central hemodynamic changes. The larger absolute increase observed in IOP (2.5 mmHg) compared to CVP (1.7 mmHg) warrants further investigation but suggests a potentially amplified or more sensitive response of the ocular system to systemic volume shifts, particularly in the context of sepsis-induced venous capacitance changes and altered fluid dynamics. This preliminary data set the stage for the correlational analysis, reinforcing the rationale for exploring IOP as a non-invasive surrogate for CVP.

At baseline, a strong, statistically significant positive correlation was identified between CVP and IOP (Figure 3). This relationship strengthened to a very strong correlation after the fluid challenge. Figure 3 presents a comprehensive summary of the correlational and predictive analyses between intraocular pressure (IOP) and central venous pressure (CVP), both at baseline and critically, after a fluid challenge in the study. The top-left panel, "Before Fluid Challenge (Baseline State Analysis)," quantifies the initial relationship.

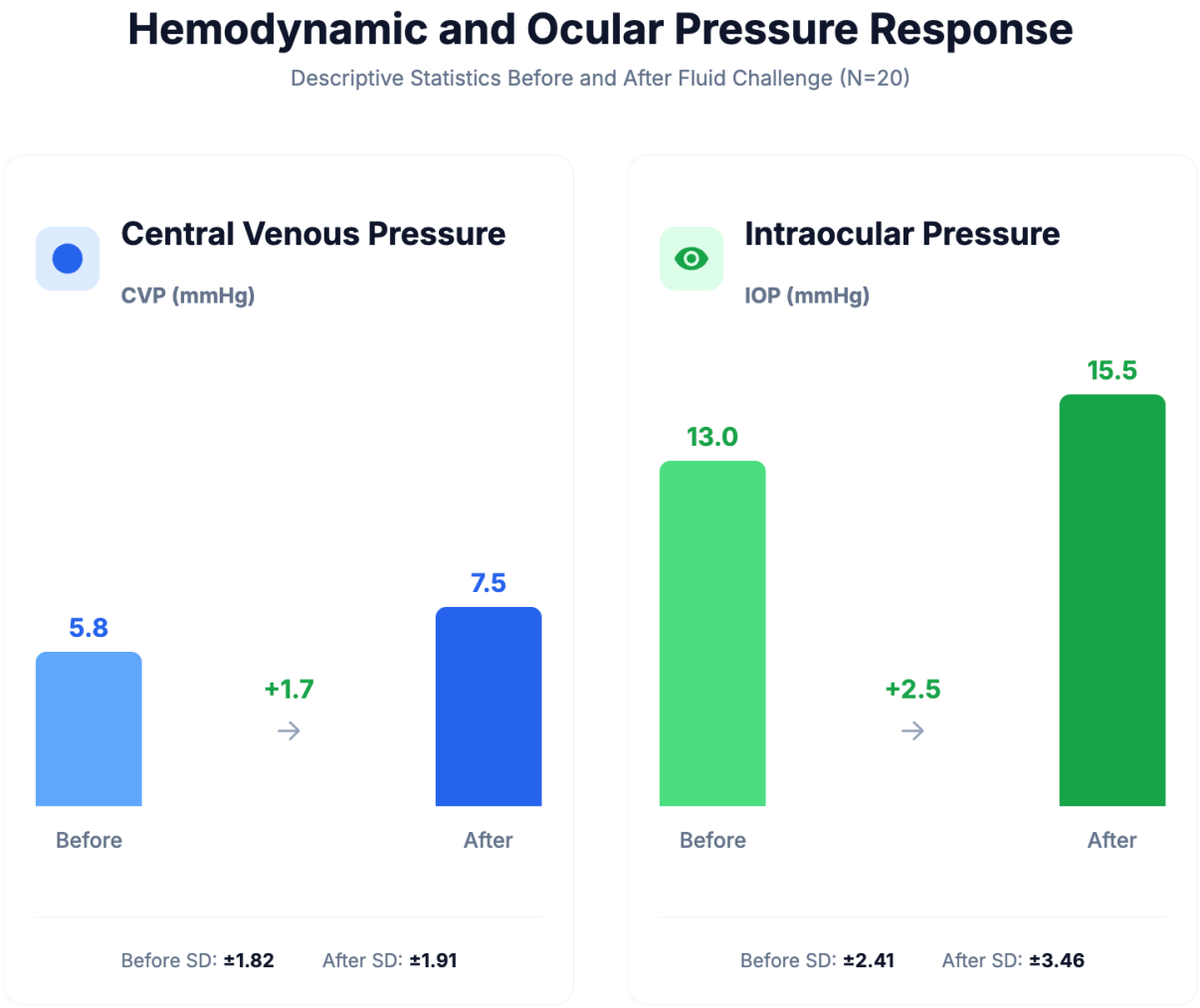

Figure 2. Descriptive statistics of CVP and IOP before and after fluid challenge.

It reveals a Pearson's r value of 0.756, indicating a strong positive correlation between CVP and IOP at baseline. This finding is statistically highly significant with a p-value of 0.001, affirming that even in the absence of acute volume intervention, a substantial direct relationship exists. The strong positive correlation suggests that as baseline CVP increases, baseline IOP tends to increase proportionally. The top-right panel, "After Fluid Challenge (Dynamic Response Analysis)," highlights the impact of the fluid intervention. Following volume expansion, the correlation between CVP and IOP remarkably strengthened, yielding a Pearson's r value of 0.947. This represents a "Very Strong Positive Correlation," underscored by an even more robust statistical significance ($p < 0.001$). The significant enhancement of the correlation post-fluid challenge is a pivotal finding, suggesting that the dynamic interplay of pressure changes after a hemodynamic perturbation makes IOP an even more reliable indicator of CVP. This finding aligns with the concept that in conditions like sepsis, where venous capacitance and endothelial integrity are altered, the transmission of central venous pressure to the ocular system becomes highly efficient. The lower, central panel, "Predictive Model (Linear Regression Analysis - Post-Challenge Data),"

illustrates the derived predictive capability based on the post-fluid challenge data, which showed the strongest correlation. The scatter plot visually displays the individual data points of CVP plotted against IOP, demonstrating a clear linear trend. A regression line, representing the best fit for these data points, is prominently featured, visually confirming the strong linear relationship. The predictive power of this model is quantified by an R^2 Value (Coefficient of Determination) of 0.890. This R^2 value indicates that 89.0% of the variance in CVP can be explained by the variance in IOP after a fluid challenge, signifying an excellent fit of the model to the data. Below the scatter plot, the "Derived Regression Equation" is presented: CVP = -0.619 + (0.522 × IOP). This formula represents the practical output of the analysis, providing a direct means to estimate CVP using a measured IOP value. Figure 3 clearly and compellingly demonstrates a robust, statistically significant, and dynamically enhanced correlation between IOP and CVP in septic patients. The high R^2 value and the explicit regression equation derived from the post-challenge data highlight the strong predictive utility of IOP, particularly when the cardiovascular system is actively responding to volume changes. This figure provides the central evidence for the potential of ocular tonometry as a viable, non-invasive method for hemodynamic assessment in critical care settings.

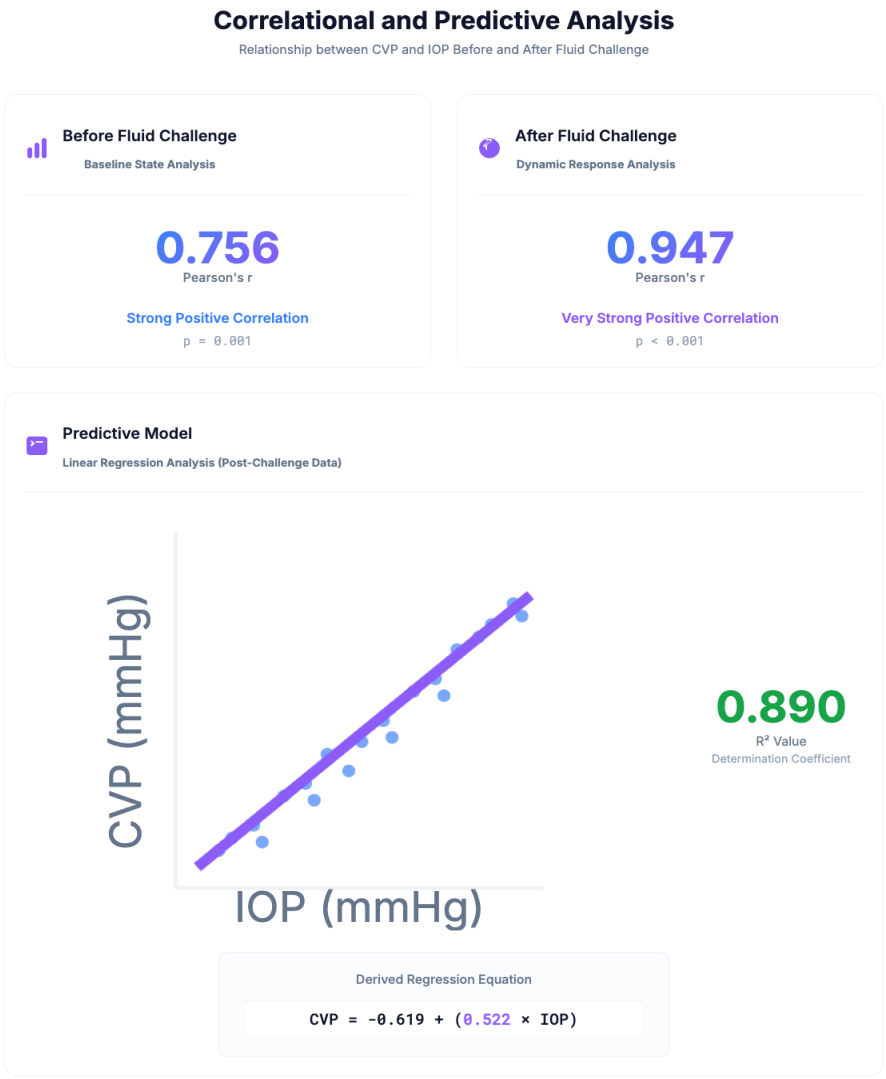

Figure 3. Correlation and predictive analysis.

4. Discussion

The results of this investigation provide compelling, albeit preliminary, evidence that intraocular pressure is a high-fidelity reporter of central venous pressure in patients with sepsis. The study successfully demonstrates a powerful physiological coherence between the ocular and central venous compartments, a link that is not only present at baseline but is dramatically amplified and clarified by a dynamic hemodynamic challenge. Figure 4 presents a meticulously crafted schematic that elegantly distills the complex pathophysiological cascade initiated by sepsis and directly links these systemic derangements to the study's central finding: a high-fidelity correlation between central venous pressure (CVP) and intraocular pressure (IOP). The cascade commences with Stage 1: Septic Insult, focusing on "Systemic Inflammation." This initial panel, marked by a vivid red icon symbolizing a generalized inflammatory response, sets the foundation for all subsequent physiological derangements. At its core, sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. It is not merely the presence of pathogens but the body's aberrant reaction to them that drives the pathology.[11] Upon recognition of microbial components (bacterial lipopolysaccharide or viral nucleic acids) by host pattern recognition receptors, a rapid and massive release of pro-inflammatory mediators is triggered. These include a diverse array of cytokines (TNF-α, IL-1β, IL-6), chemokines, and other inflammatory molecules. This "cytokine storm" propagates a widespread inflammatory cascade throughout the body, targeting various organ systems, including the cardiovascular system and, pertinently, the microvasculature of the eye. This initial stage underscores that the subsequent hemodynamic and ocular changes are not isolated events but rather downstream consequences of this fundamental, pervasive systemic inflammatory response.[12] The magnitude and persistence of this dysregulated inflammation are key determinants of septic shock severity and the consequent physiological alterations observed in the study.[13] Following the initial inflammatory trigger, Stage 2: Systemic Consequences delineates the two primary, interrelated systemic derangements that are crucial for understanding the CVP-IOP link: "Venoplegia & Passive Conduits" and "Endothelial Leak & Ocular Edema." An arrow visually connects Stage 1 to Stage 2, indicating a direct causal progression. The first critical systemic consequence, "Venoplegia & Passive Conduits," highlighted by a vibrant orange icon representing vasodilation, describes the profound alteration in venous tone characteristic of sepsis. Inflammatory mediators, particularly the robust induction of inducible nitric oxide synthase (iNOS), lead to an excessive production of nitric oxide (NO). NO is a potent vasodilator, and in sepsis, its uncontrolled release causes widespread relaxation of vascular smooth muscle, especially in the venous capacitance vessels.[14] This phenomenon, often termed "venoplegia," transforms the normally dynamic and compliant venous system into a largely passive conduit. Unlike arteries, veins are highly compliant and normally capable of adjusting their tone to regulate venous return and cardiac output. However, in septic venoplegia, this active regulation is compromised. The veins become distended and less responsive, meaning they act more like passive tubes that simply transmit pressure changes backward without significant buffering or dampening. Consequently, fluctuations in central venous pressure, particularly those induced by interventions like a fluid challenge, are transmitted more directly and efficiently retrograde through the valveless venous system (including the internal jugular veins and ophthalmic veins) towards the eye.[15] This passive transmission greatly enhances the direct mechanical coupling between CVP and IOP, explaining how changes in systemic venous pressure can directly influence ocular hemodynamics. The second critical systemic consequence, "Endothelial Leak & Ocular Edema," depicted with a striking purple icon symbolizing a compromised barrier, refers to the widespread endothelial dysfunction and increased

capillary permeability that is a hallmark of sepsis. The systemic inflammatory response damages the delicate endothelial glycocalyx, a carbohydrate-rich layer lining the inner surface of blood vessels. Degradation of this glycocalyx, coupled with direct endothelial cell injury, leads to the breakdown of endothelial tight junctions. This increased permeability causes plasma fluid and proteins to leak out of the intravascular space into the interstitial tissues, resulting in systemic and localized edema. Crucially, this capillary leak also affects the microvasculature of the eye, particularly the conjunctival and episcleral vessels. Ocular edema, even if subtle, can lead to compression of the episcleral venous plexus – the final pathway for aqueous humor outflow from the eye. Increased resistance to aqueous humor outflow directly contributes to an elevation in intraocular pressure.[16] Therefore, systemic endothelial dysfunction in sepsis contributes to elevated IOP not just through direct pressure transmission but also by impeding ocular fluid drainage, further strengthening the CVP-IOP relationship. The fluid challenge administered in the study would exacerbate this endothelial leak, causing further interstitial edema and potentially a more pronounced and congruent rise in both CVP and IOP. These two mechanisms—venoplegia enhancing pressure transmission and endothelial leak fostering ocular outflow resistance—are not independent but synergistically contribute to the robust CVP-IOP coupling observed in septic patients. The culmination of these pathophysiological processes is presented in Stage 3: Oculovascular Outcome, directly integrating the study's primary finding into the physiological narrative. This final panel, prominently featuring a blue icon for CVP and a green icon for IOP, is titled "Study Finding: High-Fidelity Correlation," and explicitly states "r = 0.947"—the very strong Pearson's correlation coefficient found after the fluid challenge. This numerical result is visually anchored by a double-headed arrow labeled "Valveless Venous Pathway," reinforcing the anatomical and physiological link. This stage synthesizes how the systemic consequences of sepsis create an environment where IOP becomes a highly sensitive and accurate reflection of CVP. The combined effects of increased venous compliance (venoplegia) and generalized microvascular permeability (endothelial leak) converge to make the ocular venous system an unbuffered extension of the central venous system. Enhanced Pressure Transmission: The venoplegia ensures that pressure waves originating from the right atrium and transmitted through the vena cava, internal jugular veins, and finally into the valveless ophthalmic veins are efficiently and directly conveyed to the episcleral venous system, which directly impacts IOP. The loss of venous tone means there is minimal dampening of these pressure fluctuations as they travel towards the eye. Augmented Outflow Resistance: The generalized endothelial leak causes interstitial edema in various tissues, including the delicate structures around the eye. This edema increases resistance to aqueous humor outflow by compressing the episcleral venous plexus. Since IOP is determined by the balance of aqueous humor production and outflow, increased outflow resistance directly leads to a rise in IOP. Furthermore, the episcleral venous pressure (EVP) is a direct determinant of IOP, and EVP is itself highly correlated with CVP.[17] In sepsis, both the direct pressure transmission from CVP to EVP and the indirect effect of increased tissue pressure around the ocular drainage system contribute to an elevated IOP. Dynamic Responsiveness: The study's use of a fluid challenge proved particularly insightful here. In a healthy individual, compensatory mechanisms might buffer the relationship between a sudden volume load, CVP, and IOP. However, in septic shock, these compensatory mechanisms are overwhelmed or dysregulated. The passive nature of the septic venous system, combined with the increased susceptibility to edema, means that a rapid increase in intravascular volume (from the fluid challenge) translates almost directly into a proportional increase in both CVP and IOP. This dynamic response explains why the correlation strengthened from 0.756 at baseline to an exceptionally strong 0.947 post-challenge—the fluid

bolus effectively "stressed" the system, revealing the true, unbuffered relationship. This high R-squared value (0.890) derived from the post-challenge data, which means 89% of CVP variance is explained by IOP variance, underscores the profound clinical potential. Figure 4 articulates that sepsis creates a unique physiological state where the ocular compartment, through its intricate and valveless venous connections to the central circulation, acts as a transparent window. The systemic inflammatory response breaks down normal physiological buffers, allowing CVP to exert a more direct and unattenuated influence on IOP. This pathophysiological understanding not only validates the empirical findings of the study but also positions ocular tonometry as a highly logical and mechanistically sound method for monitoring central venous hemodynamics in the complex environment of septic shock. The figure effectively translates complex biology into a clear, actionable insight, emphasizing the scientific rigor underpinning the novel CVP-IOP relationship discovered.[18]

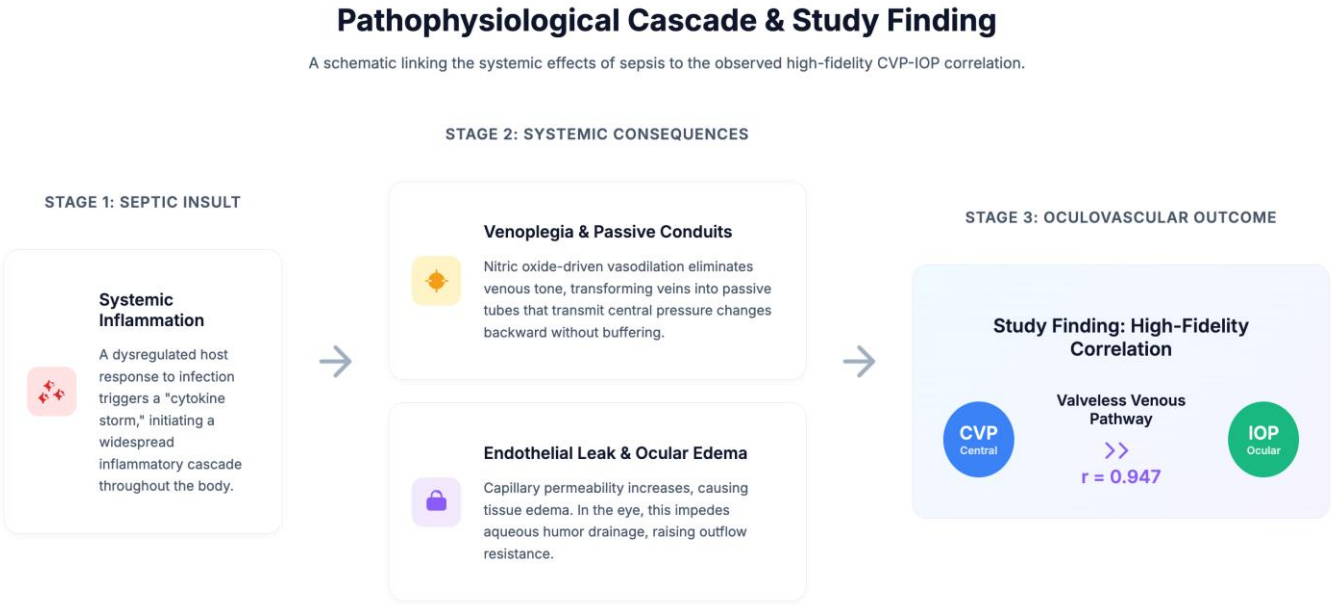

Figure 4. Pathophysiological cascade & study finding.

A critical appraisal of this study must begin with a reflection on its target variable: Central venous pressure. The manuscript's premise is to find a non-invasive surrogate for CVP, yet it is imperative to acknowledge that CVP itself is a deeply flawed and controversial parameter. The historical view of CVP as a reliable indicator of preload and a direct guide for fluid administration has been largely dismantled by a decade of clinical evidence. A patient's position on their Frank-Starling curve cannot be reliably inferred from a single CVP value. Therefore, the goal of this research should not be interpreted as simply finding an easier way to measure a problematic number. Instead, we propose a more nuanced interpretation. The clinical utility of CVP in contemporary practice has shifted towards its role as an indicator of venous congestion and a safety marker for fluid resuscitation. A very low CVP may suggest that fluid administration is likely safe, while a high or rapidly rising CVP serves as a crucial alarm, signaling that the right heart's capacity to handle further volume is limited and that continued fluid loading may precipitate organ edema and harm. From this perspective, the objective of a CVP surrogate is not to predict fluid responsiveness,

but to provide a non-invasive window into right-sided filling pressures and the state of systemic venous congestion. Our study should be viewed through this modern lens. The strong correlation found suggests that IOP may indeed function as a non-invasive "venous congestometer," inheriting not only CVP's information but also its limitations. The key advantage, however, remains the circumvention of the significant risks associated with invasive catheterization.[19]

The septic state is a unique physiological milieu that appears to unmask and enhance the CVP-IOP relationship. This can be attributed to several synergistic pathophysiological processes. First, the hallmark of septic shock is profound systemic vasodilation, driven largely by the massive upregulation of inducible nitric oxide synthase (iNOS). This results in a loss of venomotor tone, transforming the normally compliant and reactive venous system into a more passive, low-resistance set of conduits. In this state of "venoplegia," the backward transmission of pressure waves from the right atrium through the valveless jugular and ophthalmic veins is likely to be more direct and less buffered compared to a healthy state with intact vascular tone. This provides a compelling physiological explanation for the exceptionally strong correlation coefficients observed in our cohort. Second, sepsis is characterized by widespread endothelial injury and the degradation of the endothelial glycocalyx. This protective lining of the vasculature is shed, leading to a dramatic increase in capillary permeability. In the eye, this "capillary leak" phenomenon can manifest as conjunctival and episcleral edema. This interstitial fluid accumulation can physically compress the delicate episcleral venous plexus—the final outflow channel for aqueous humor. This sepsis-induced increase in outflow resistance would theoretically make the IOP more sensitive to even small changes in the downstream pressure of the central venous system. Third, patients with sepsis, particularly those requiring significant fluid resuscitation, are at high risk of developing intra-abdominal hypertension (IAH). Elevated intra-abdominal pressure physically compresses the inferior vena cava, impeding venous return and artificially elevating CVP. Simultaneously, IAH impedes venous drainage from the head and orbit, directly increasing IOP. Therefore, IAH acts as a common-cause confounder that would paradoxically strengthen the statistical association between CVP and IOP, linking them through a shared pathology of venous outflow obstruction. While we did not measure intra-abdominal pressure, its high prevalence in this population likely contributed to the robust correlation we observed. IOP, in this context, may serve as a valuable, non-invasive indicator of the systemic consequences of IAH.[20]

The most significant finding of this study is the marked strengthening of the CVP-IOP correlation after a fluid challenge. This highlights that a dynamic assessment provides a clearer signal than a static one. The administration of a fluid bolus acts as a physiological stress test on the entire venous system. The resulting change in pressure (ΔCVP) for a given change in volume (the fluid bolus) is an expression of the system's venous compliance. Our data show that the change in IOP (ΔIOP) tracks this ΔCVP with extraordinary fidelity (r=0.947). This shifts the potential clinical application of this technique. Rather than focusing on a single IOP measurement to estimate a single CVP value, the true utility may lie in trending the change in IOP in response to a therapeutic maneuver. For instance, a clinician administering a 250 mL fluid bolus and observing a 4 mmHg rise in IOP could infer that CVP has risen by approximately 2 mmHg, suggesting that the venous system is becoming less compliant. This aligns perfectly with the modern paradigm of assessing fluid responsiveness, where the dynamic response to a fluid challenge is of far greater interest than the pre-challenge static numbers. Ocular tonometry could thus evolve into a tool for performing a "non-invasive fluid challenge," providing insights into venous compliance without the need for a central line.[18,19]

While the findings are provocative, they must be interpreted with significant caution due to several

major limitations. The most pressing is the very small sample size. A cohort of 20 patients is insufficient to develop a universally generalizable predictive formula. A few patients with atypical physiology could disproportionately influence the regression model. Therefore, the derived equation, CVP = -0.619 + (0.522 x IOP), must be considered preliminary and hypothesis-generating. It serves as a proof-of-concept and a quantitative estimate of the relationship in this specific cohort, but it absolutely requires validation in larger, multi-center trials before it could ever be considered for clinical use. Second, the fluid challenge protocol, allowing a range of 250-500 mL, introduced a degree of variability in the hemodynamic stimulus. Although a median volume was reported, this lack of strict standardization introduces potential noise into the data. Future validation studies should employ a standardized, weight-based fluid bolus to ensure a consistent physiological probe. Third, our exclusion of patients on PEEP > 5 cmH_2O, while methodologically necessary to isolate the CVP-IOP relationship, significantly limits the applicability of our findings. Many of the sickest sepsis patients, particularly those with acute respiratory distress syndrome (ARDS), require higher levels of PEEP. Elevated mean airway pressure directly increases both CVP and IOP, and the nature of this interaction likely alters the simple linear relationship we observed. Our model is therefore only applicable to a subset of the septic population on low ventilatory support. Finally, the study did not account for the heterogeneity of sepsis phenotypes. We did not differentiate between patients with hyperdynamic, vasoplegic shock and those with septic cardiomyopathy. These distinct physiological states could plausibly exhibit different CVP-IOP relationships. Future studies should aim to characterize these phenotypes to determine if the correlation holds true across the spectrum of septic circulatory failure.

5. Conclusion

In this prospective observational pilot study, we have demonstrated a powerful and physiologically coherent correlation between intraocular pressure and central venous pressure in a cohort of critically ill patients with sepsis. This relationship strengthens to a remarkable degree following a dynamic fluid challenge, suggesting that ocular tonometry could serve as a high-fidelity, non-invasive tool for tracking changes in right-sided filling pressures and systemic venous congestion. The profound pathophysiological derangements of sepsis, rather than obscuring this connection, appear to create a state that amplifies it, making the eye a potentially valuable window into central hemodynamics. However, the findings must be interpreted with significant scientific caution. The derived predictive formula is preliminary and hypothesis-generating, born from a small, single-center cohort. It is not intended for clinical application at this stage. Rather, this research should be viewed as a robust proof-of-concept that lays the essential groundwork for future, larger-scale validation trials. Should these findings be replicated, ocular tonometry could one day find its place in the critical care armamentarium as a simple, safe, and accessible method to complement the hemodynamic assessment of septic patients, embodying a true paradigm shift from invasive, risk-prone procedures to non-invasive, physiologically-informed monitoring.

6. References

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