Review Article

Relevance of Microvascular Flow Assessments in Critically Ill Neonates and Children: A Systematic Review

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Objectives: Resolution of impaired microvascular flow may lag the normalization of macrocirculatory variables. The significance of microcirculatory dysfunction in critically ill children and neonates is unknown, but microcirculatory variables can be measured using Doppler or videomicroscopy imaging techniques. We outline the current understanding of the role of the microcirculation in critical illness, review methods for its assessment, and perform a systematic review of how it has been monitored in critically ill neonates and children.

Design: Systematic review (PROSPERO CRD42019117993).

Setting: Not applicable.

Subjects: Not applicable.

Interventions: None.

Measurements and Results: We systematically searched MEDLINE, EMBASE, PubMed, and Web of Science. We included studies of critically ill patients 0 to 18 years old investigating microcirculatory blood flow. Two reviewers analyzed abstracts and articles. Results were qualitatively analyzed due to study heterogeneity. A total of 2,559 abstracts met search criteria, of which 94 underwent full-text review. Of those, 36 met inclusion criteria. Seven studies investigated microcirculatory changes in critically ill children. Twenty studies investigated the microcirculatory changes in neonates with variable diagnoses compared with a diverse set of clinical endpoints. Nine studies assessed the effects of age, sex, and birth weight on microvascular flow in neonates. Across all studies, microcirculatory dysfunction was associated with poor outcomes and may not correlate with observed macrovascular function.

Conclusions: Assessment of microvascular flow in critically ill children and neonates is possible, although significant challenges remain. In many such patients, microvascular blood flow is disrupted despite medical management targeting normalized macrovascular variables. Future studies are needed to define normal pediatric microvascular flow variables and to assess the impact of patient and treatment factors on its function. (*Pediatr Crit Care Med* 2020; 21:373–384)

Key Words: capillary leak; children; critical illness; endothelial dysfunction; microcirculation; shock

The microcirculation is a critically important and potentially underappreciated component of the cardiovascular system. This dynamic vascular segment resides between the arterioles and venules and is comprised of precapillary arterioles, capillaries, and postcapillary venules (1, 2). These vessels are less than 100 μm in diameter, smaller than a human hair. The microcirculation consists of endothelial cells and associated supporting cells. Precapillary arterioles are surrounded by smooth muscle cells (SMCs), which act to regulate blood flow to tissue. Capillaries and postcapillary venules are supported by pericytes and less frequent SMCs (3, 4). Capillaries, the smallest of these vessels range between 3 and 6 μm in diameter, are the most numerous and dynamic part of the microcirculation (5, 6). These tiny vessels are responsible for the delivery of nutrients and signaling molecules, removal of waste products, flux of intravascular fluid, and heat exchange at the level of individual cells (7, 8). These processes require intimate contact, and consequently, a single capillary may be responsible for supporting a layer of only two or three parenchymal cells (9, 10).

All blood flow is dictated by pressure gradients. In the microcirculation more specifically, the difference between precapillary hydrostatic pressure (P_{cap}) and postcapillary venular pressure (mean systemic filling pressure [P_{msf}]) drives flow. Under normal conditions, P_{cap} is dictated by precapillary SMC sphincter tone, subject to tissue-specific autoregulation which is, in part, regulated by capillary pericytes (11). Regulation of P_{msf} is dictated by venous volume and compliance of the larger

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venules and veins (12). Normal microcirculatory flow is characterized by homogenous RBC density and velocity throughout the length of the capillary, with precapillary oxygen tension (Po_2) of 90 mm Hg and postcapillary Po_2 of 45 mm Hg. The transit time for a RBC in capillaries is highly variable across different organs (13).

In times of physiologic stress, the microcirculation adapts to meet increased tissue metabolism by three mechanisms. First, oxygen extraction is increased throughout the length of the capillary. This adaptation is passive and results in decreased central venous oxygen saturation. Second, greater cardiac output augments microvascular flow decreasing RBC transit time and boosting the total number of RBCs crossing the capillary per unit time. Last, most tissues have excess capillaries to augment perfusion during times of greater need. The relative perfusion of specific capillary networks is controlled by autonomic nervous system activity (neurogenic), small molecule autocrine signaling (metabolic), and pressure-dependent autoregulation (myogenic) of the precapillary SMCs and pericytes (3). Microvascular pericytes, in particular, are essential in the regulation of capillary diameter (14), barrier function (15), basement membrane properties (16), and endothelial sprouting (17), all essential functions to maintain adequate flow to support parenchymal cells. Increased capillary recruitment reduces the distance between perfused capillaries and lessens the distance for oxygen to diffuse. These compensatory mechanisms vary by organ. For example, the heart and diaphragm have no recruitable capillaries, whereas this is the predominate adaptive method in skeletal muscle (18).

In times of pathophysiologic stress, such as shock, microvascular flow may be disrupted with a number of deleterious consequences. Although confirmatory evidence is limited, there are several proposed mechanisms by which the microcirculation may become altered (19). Since the microvasculature is responsible for oxygen and nutrient delivery, perturbations in capillary flow result in organ hypoperfusion. In late stages of shock, cellular hypoxia is evidenced by increased markers of perfusion inadequacy, such as increasing serum lactate or organ-specific enzymes. Blockage of capillaries results in an inappropriately heterogeneous microvascular flow (**Fig. 1**, number 1), with flow diverted through pathologically dilated capillaries, leading to microvascular shunt (20, 21). Hemodilution, which may result from volume resuscitation, reduces the number of RBCs in each capillary decreasing oxygen content (Fig. 1, number 2). In the setting of venous congestion, such as occurs in cardiogenic shock, P_{msf} rises and impairs flow and oxygen delivery (Fig. 1, number 3). Finally, tissue edema, in the setting of capillary leak, expands the distance that oxygen must diffuse to reach cells, producing cellular dysoxia and dysfunction (Fig. 1, number 4). Tissue-specific capillaries have different responses to the above pathophysiologic processes. This heterogeneity of function makes it impossible to extrapolate findings from a single capillary to the system as a whole and thus undermines our understanding of global microvascular function (22).

Monitoring of microvascular function is challenging since the common macrovascular variables followed (e.g., blood pressure [BP], heart rate [HR], central venous

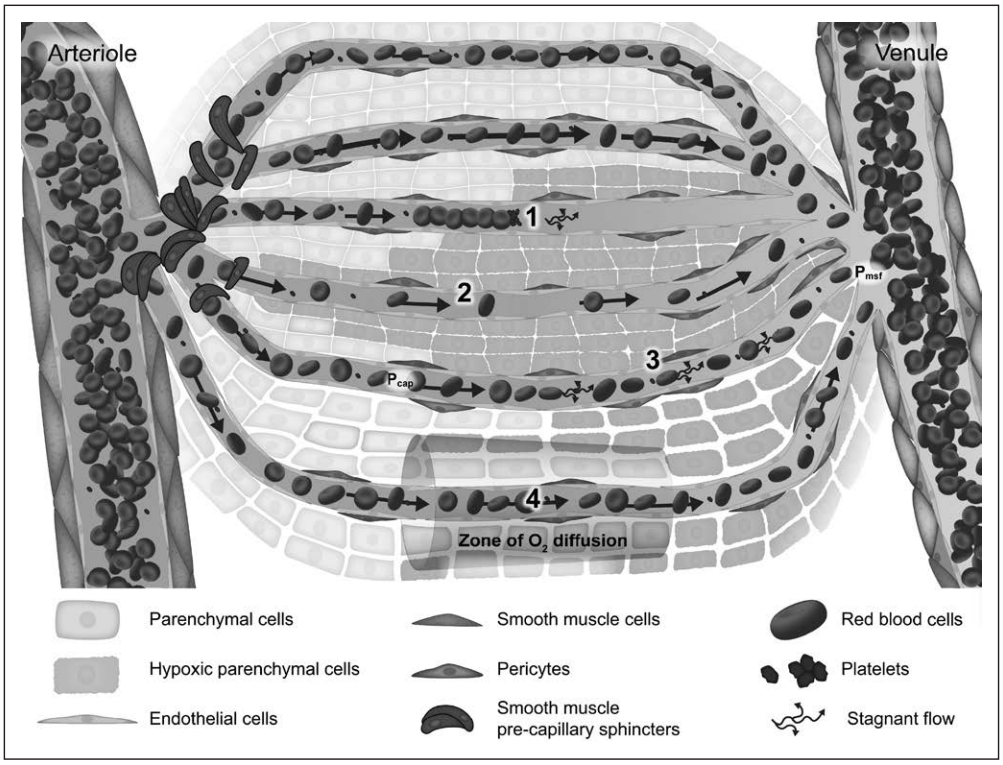

Figure 1. Microcirculatory blood flow and its pathologic alterations. Normal microvascular blood flow is determined by precapillary smooth muscle cell (SMC) tone. Physiologic flow, illustrated by the block arrows, provides oxygen tension sufficient for cellular homeostasis along the entire capillary, as shown in the top two capillaries. Pathophysiologic microvascular flow, resulting in inadequate cellular oxygen delivery, may occur through four proposed mechanisms. 1) Capillaries may be blocked by platelet microthrombi, leukocyte plugs, nondeformable RBC, or precapillary SMC dysfunction. Obstruction produces blockage to flow, resulting in cellular hypoxia distal to the obstruction and increased flow heterogeneity, as blood flow will be redirected to open capillaries, creating tissue-level shunting. 2) Hemodilution as seen after cardiopulmonary bypass or massive volume resuscitation, may result in cellular hypoxia despite appropriate flow. 3) Increased venous pressures, from rising central venous pressure, or postcapillary tamponade from increased tissue hydrostatic pressure. This produces and increase in mean systemic filling pressure (P_{msf}) with little change in the capillary hydrostatic pressure (P_{cap}) thereby decreasing driving pressure for capillary flow (P_{cap}–P_{msf}). This results in rapid decrease is oxygen tension and cellular hypoxia. 4) Tissue edema, from capillary leak or massive volume resuscitation, increases the distance for oxygen to diffuse resulting in cellular hypoxia despite adequate flow. Multiple problems may be present in a single capillary network and their effects may overlap, exacerbating organ dysfunction.

pressure [CVP], and cardiac index) may have limited relevance. "Hemodynamic coherence" is a term that describes the extent to which normal macrovascular function correlates with appropriate microvascular function (23). Multiple studies in adults have demonstrated that hemodynamic coherence may be lost in critically ill humans (23, 24). Furthermore, persistent microvascular dysfunction has been associated with organ dysfunction and death in adults (25). Nonetheless, goal-directed resuscitation of children in shock typically targets macrovascular hemodynamic goals, assuming that hemodynamic coherence is intact. Yet, specific treatment strategies, such as fluid resuscitation or vasopressor therapy, may improve macrovascular variables (such as CVP) to the detriment of microvascular flow (by decreasing P_{cap}–P_{msf}) (26).

Microcirculatory function can be directly assessed in several ways. Videomicroscopy permits the observation of the number of RBCs and their velocity through individual capillaries (**Table 1**). These devices use dark-field microscopy where polarized light at 550 nm is preferentially scattered by the hemoglobin in RBCs. The scattered light is captured for analysis and produces short video clips of illuminated capillary networks on dark backgrounds. Recent advances in optics have resulted in more precise instruments, from orthogonal polarized spectral (OPS), side-stream dark field (SDF), and incident dark field (IDF) imaging. These devices, notably IDF, are state of the art for current research. Other technologies include laser Doppler flowmetry (LDF) which measures the relative velocity of RBC flow through sections of tissue from the Doppler shift of laser focused light (700 to 1,000 nM). Finally, intravital microscopy and capillaroscopy use light microscopy to visualize flow velocity through capillary loops, although in humans, this technology is usually limited to the nailbed. Since the ultimate aim of resuscitation is to restore adequate cellular oxygen delivery, monitoring the microcirculation may provide the most pertinent measures (**Table 2**) (24). However, microcirculatory function is difficult to assess in critically ill children. A major challenge is clinical feasibility. OPS requires an external light source and is prone to blurring, blockage, or difficulty positioning the device. SDF performs better but still requires manual intervention and scoring systems. Both of these methods are sensitive to motion artifacts. Some of the devices are quite bulky, and all require training and expertise to obtain and interpret measurements. Newer devices are smaller and more intuitive with the promise of automated data analysis that may be more amenable to pediatric studies. A more significant concern is the sampling location. Monitoring oral microcirculation may not provide information on perfusion of central, more essential organs (33). Obstructed or heterogeneous flow may be present in one organ and not in another. Another major impediment is the lack of normal pediatric values, complicating interpretation of image analysis in children and infants. Indirect assessments, such as near-infrared spectroscopy or arterio-venous P_{CO_2} differences, can provide insight into the global function of the microvasculature relative to metabolism.

A better understanding of microcirculatory responses may result in more effective treatments for common conditions such as shock. The extent to which microvascular flow and hemodynamic coherence are disrupted by critical illness in children is much less well defined than in adults. The purpose of this review to gain a deeper understanding of this issue. Therefore, we performed a systematic review to assess the current state of research into microvascular dysfunction in critically ill children and neonates.

MATERIALS AND METHODS

Search Strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (34). Our study protocol is

TABLE 1. Types of Microvascular Imaging Devices

Assessment Technique and Reference	Application and Site of Assessment	Variables Measured	Limitations to Use	Examples of Commercial Available Devices
Videomicroscopy: Orthogonal polarization spectral imaging (27), side-stream dark field imaging (28), incident dark field imaging (29)	Direct viewing of buccal or sublingual microcirculation	Total vessel density, functional capillary density, proportion of perfused vessels, proportion of small perfused vessels, microcirculatory flow index, microcirculatory heterogeneity index	Image acquisition affected by operator skill Image analysis performed offline	MicroScan CapiScope CytoCam
Doppler: Laser Doppler flowmetry (30), laser Doppler perfusion measurement (31)	Microcirculatory functional integrity assessment of superficial tissue	Relative flow, Microvascular hemoglobin content, Microvascular integrity	Does not differentiate between microvascular segments (i.e., arteriole, capillary, and venule)	Blood FlowMeter Vein Finders
Microscopy: Intravital microscopy (32)	Nailbed microscopy	Capillary density	Nailfold area only, unsuitable for critically ill patients	CapiScope

TABLE 2. Variables That Can Be Measured to Describe the Microcirculation

Microcirculatory Variables	Units	Significance
Vessel diameter	μm	Small < 10 μm, medium 10–20 μm, large > 20 μm
TVD	mm/mm^2 (1/mm)	Measure of all vessels in a field of view. Total length of vessels (small, medium, or large) divided by total area of the field of view
Perfused vessel density	mm/mm^2 (1/mm)	PPV multiplied by TVD
PPV	% vessels perfused	Percentage of perfused vessels in a given image quadrant obtained. Calculated by total length of perfused small vessels divided by total length of small vessels
MFI	Continuous (normal), sluggish (slow), intermittent or absent (no flow)	Qualitative assessment of flow over quadrants. An average of images obtained
Heterogeneity index	Arbitrary unit	Measure of flow heterogeneity. Maximum MFI quadrant minus minimum MFI quadrant divided by mean MFI
De Backer score	Vessels/mm	Alternate for TVD, using standard grid format with three equally spaced vertical and horizontal lines. Calculated as number of vessels crossing grid lines divided by the total length of the lines
Oxygen saturation	% hemoglobin saturation	Tissue oxygenation for a specific organ studied, i.e., kidneys
Microvascular flow velocity	μm/s	Can differentiate speeds between small, medium and large vessels

MFI = microcirculatory flow index, PPV = proportion of perfused vessels, TVD = total vessel density.

In general, the variables targeted are assessments of vessel recruitment (functional capillary density, perfused vessel density, PPV) or the character of flow through those vessels (MFI, heterogeneity index, microvascular flow velocity). Not all devices can measure all variables, and no pediatric normal values have been established.

registered in the PROSPERO database of systematic reviews, CRD42019117993 (**Supplementary Table 1**, Supplemental Digital Content 1, http://links.lww.com/PCC/B141). We began our search with the Yale MeSH Analyzer (35), using key articles to refine the search strategy for the concepts critical illness, microcirculation, and children (**Supplementary Table 2**, Supplemental Digital Content 2, http://links.lww.com/PCC/B142). In each database, we performed search queries and used an iterative process to translate and refine the searches. All searches were limited to the English language. Searches in EMBASE and MEDLINE were limited using the human filter. Additional articles were identified by examining other systematic reviews, reference lists, bibliographies, and preidentified websites such as National Institutes of Health reporter, conference abstracts (Web of Science), and publicly available internet searches (Google Scholar).

On December 6, 2018, the authors searched PubMed (conception through December 06, 2018), MEDLINE (Ovid MEDLINE ALL 1946 to December 06, 2018), EMBASE (Ovid EMBASE 1974 to 2018 December 07), and Web of Science (conception through December 06, 2018). On March 14, 2019, a second search was completed in Ovid MEDLINE ALL, Ovid EMBASE, PubMed, and Web of Science Core Collection. The search repeated the controlled vocabulary terms and free-text terms. Manuscripts identified from these searches were deduplicated in EndNote X8 (Clarivate Analytics, Philadelphia, PA) and uploaded to Covidence (36).

Study Selection

Two independent reviewers (L.M., E.N.) completed title, abstract, and full-text screens (**Fig. 2**). The senior author (R.P.) mediated consensus meetings to resolve discrepancies. Studies were screened for meeting the inclusion criteria: 1) Observational case report, cohort, case control, or clinical trial studies; 2) Studies involving critically ill pediatric patients; and 3) Studies assessing microcirculatory flow. Since a continuum of disease states exist under the definition of critical illness, there is not one single condition that satisfies our query. Our search strategy (Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/PCC/B142) includes many terms associated with critical illness. For including or excluding studies in ambiguous cases, we relied on the primary authors definition or assessment of the study participants' "critically ill status." Studies investigating animal or human cellular models as well as those that did not specifically assess microcirculatory flow were excluded.

Assessment of the Evidence and Data Abstraction

All collected studies were reviewed using the Quality In Prognostic Studies (QUIPS) tool to assess risk of bias in prognostic factors studies from the Cochrane Review Group (37). A quantitative meta-analysis was not performed for several reasons. Relative estimates of effect could not be calculated for case series and studies that lacked control groups. Methodological heterogeneity, such as the type of assessment, the timing

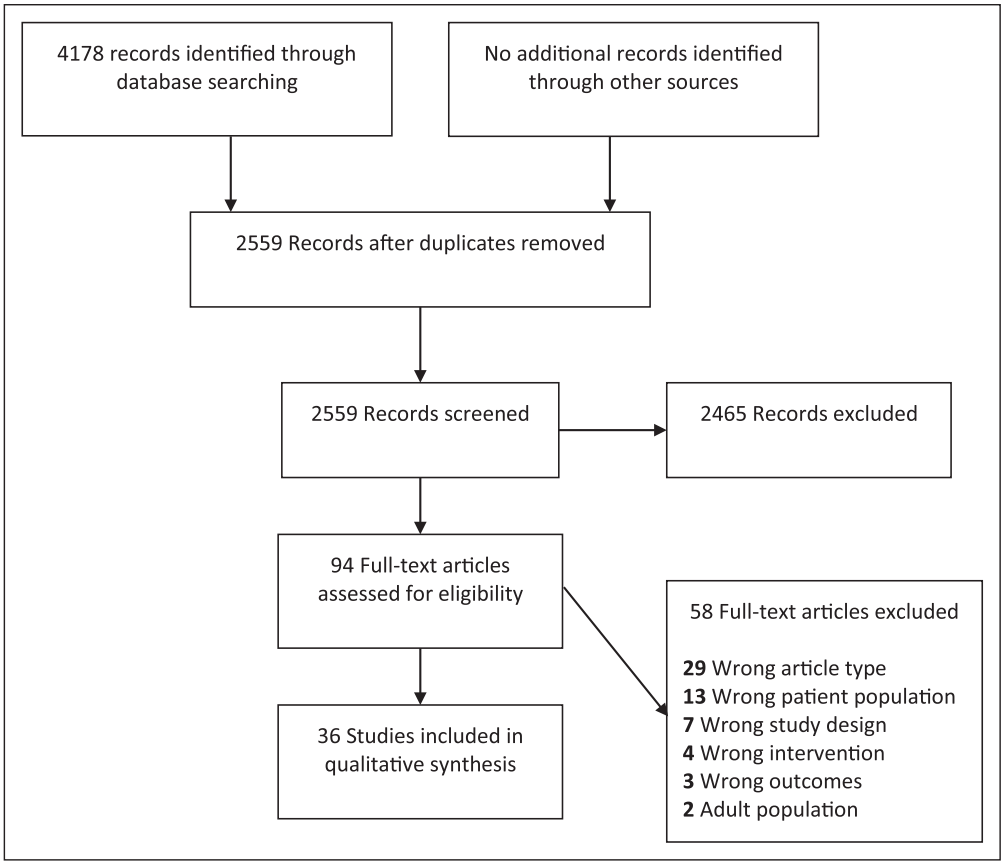

Figure 2. Study flow diagram and selection of eligible articles.

of assessment relative to disease onset, and the wide range of patient and treatment factors further prohibited quantification of results. Therefore, all studies were qualitatively analyzed.

RESULTS

A total of 4,178 citations were retrieved, pooled, and deduplicated to 2,559. Of these, 94 articles met requirements for full-text review, after which 36 studies were included in the investigation for evaluation of microcirculatory flow: seven assessing critically ill children and 29 involving neonates.

Overall, the quality of the evidence for using microvascular assessment to predict outcomes is low. Of the 27 studies included, eight rated as low, 18 as medium, and one as high quality (**Supplemental Table 3**, Supplemental Digital Content 3, http://links.lww.com/PCC/B143). One limitation of feasibility and generalizability was study design, as only a single randomized controlled trial involving 12 total neonates was identified (38). All other studies were observational trials or case reports. Studies assessed had low numbers of subjects, and most lacked control groups. Only 20 of the 36 studies included control patients and 28 of the 36 studies involved 40 or less subjects. In all cases, primary data could not be completely reviewed. High subject dropout rate, lack of standardized of normal values, timing and method of assessment, variables measured and comparators further downgraded the quality of the available evidence.

We identified seven studies of microcirculation in critically ill children (**Table 3**). Of these, three investigated microcirculatory flow in sepsis and found decreased microcirculatory flow index (MFI) and reduced functional capillary density and proportion of perfused vessels (PPV), using OPS or SDF with sublingual or buccal mucosa sampling (39–41, 44). These variables correlated with increased inflammatory markers and improved over time with the patient condition. Two studies investigated the effects of cardiopulmonary bypass (CPB) on microcirculatory flow. CPB appeared to minimally alter baseline microvascular variables during the procedure (43) but did negatively affect induced hyperemic response, while measuring microvascular vasodilation with cutaneous vascular conductance, intraoperatively (45). A single study investigated children after cardiac arrest and demonstrated decreased flow and perfused vessel density (PVD), which improved as patient condition recovered (42). Finally, a study using SDF sublingual sampling and investigating all-comers to the PICU found decreased MFI, PPV, and PVD that correlated with low BP and mixed venous saturation and improved after macrocirculatory normalization (32).

We identified, 29 studies involving neonates, with 20 studies relating microcirculatory flow to critical illness (**Table 4**) and nine studies relating microcirculatory flow to gender or postnatal age (**Supplementary Table 4**, Supplemental Digital Content 4, http://links.lww.com/PCC/B144). The 20 studies investigating microcirculatory changes in neonates included 300 unique patients of which 94 were full term, 82 were preterm, and 124 had no gestational age reported. Included studies related flow to a variety of etiologies of critical illness, including acute respiratory distress syndrome (ARDS), sepsis and hypoxic-ischemic encephalopathy (HIE, four studies each), CPB (three studies), and congenital diaphragmatic hernia, anemia, hypotension, and patent ductus arteriosus (a single study each).

Neonates with sepsis demonstrated a decreased hyperemia response (46, 47), skin flow (57), and functional vessel density (FVD) (50). Reactive hyperemia response refers to skin perfusion time, measuring velocity of RBCs with laser Doppler, pre- and post-arterial occlusion. Vessels in neonates with sepsis

took longer to establish perfusion in the venules postocclusive stimulus as opposed to healthy newborns. Similarly, neonates with ARDS demonstrated decreased FVD (49, 52, 63) as evidenced by OPS and SDF imaging on skin or mucosal surfaces. Reduced flow and vessel density variables were detected in neonates with congenital heart disease (51) and those undergoing CPB (58, 61), although the cerebral circulation was not affected allowing oxygen delivery to the brain to be preserved (64). Neonates undergoing therapeutic hypothermia for HIE demonstrated decreased flow variables that improved with rewarming (54, 56, 60). Additionally, decreased vessel density was associated with a rise in systemic inflammatory markers (59). Among a general population of critically ill neonates, FVD improved after blood transfusion (48). However, neither

TABLE 3. Studies of Microvascular Function in Critically Ill Children

References	Design	Critically Ill Patients	Control Patients	Method of Assessment	Site of Assessment	Quality Assessment	Major Findings
Top et al (39)	POC	15 survivors Three nonsurvivors	0	Orthogonal polarization spectral imaging	Buccal mucosa	Medium	Children who died from septic shock had initially increased then decreased FCD (3.2 cm/cm^3, 0.8–3.8, to 1.9 cm/cm^3, 1.0–2.1) compared with controls (1.7 cm/cm^3, 0.8–3.4, to 4.3 cm/cm^3, 2.1–6.9). FCD and MFI remained low despite correction of heart rate and blood pressure
Paize et al (40)	POC	20	40	SDF	Sublingual mucosa	Medium	Children with severe meningococcal disease have significant reduction in MFI, PPV, and PVD that correlated with elevated markers of endothelial origin and predicted ventilatory support requirements. MFI and PPV normalized preextubation
Caixeta et al (41)	Case report	Two	0	SDF	Sublingual mucosa	Low	Children with dengue shock were found to have low capillary flow velocity, PVD, PPV, and MFI. Patient 2 had increased PPV on day 2 but low flow resulting in persistent tissue hypoperfusion
Buijs et al (42)	POC	11 survivors Nine nonsurvivors	20	SDF	Buccal mucosa	Medium	Children receiving hypothermia after cardiac arrest had decreased PVD NS, PPV NS, MFI NS, and MFI small vessels (Ø ≤ 10 μm) that were associated with mortality risk. Perfusion improves after rewarming. Improvement in microcirculatory variables coincided with improvements in arterial lactate and o_2 tension
Scolletta et al (43)	POC	17 acyanotic Seven cyanotic	0	SDF	Sublingual mucosa	Medium	Children undergoing congenital heart surgery with cardiopulmonary bypass had generally stable TVD, PVD, and PPV for acyanotic lesions and lower TVD, PVD, and PPV for cyanotic lesions. There was weak inverse correlation between RBC storage time and MFI

(*Continued*)

TABLE 3. (*Continued*). Studies of Microvascular Function in Critically Ill Children

References	Design	Critically Ill Patients	Control Patients	Method of Assessment	Site of Assessment	Quality Assessment	Major Findings
Gonzalez et al (44)	POC	18	0	SDF	Sublingual mucosa	Medium	In children admitted to the ICU for any reason, MFI, heterogeneity index, PPV, and PVD correlate positively with systolic arterial pressure, arterial o_2 tension, temperature, and central venous saturation and negatively with central venous pressure and serum lactate
Ugenti et al (45)	Cross-sectional observational study	61 cyanotic 39 acyanotic	0	Laser Doppler perfusion monitoring	Forehead skin	Low	Microvascular skin flow is similar in patients with cyanotic and acyanotic heart disease. Local thermal hyperemia response was blunted while patients were on cardiopulmonary bypass

FCD = functional capillary density, MFI = microvascular flow index, NS = non-small vessels (Ø 11–100 μm), POC = prospective observational cohort study, PPV = proportion of perfused vessels, PVD = perfused vessel density, SDF = side-stream dark field imaging, TVD = total vessel density.
See Supplemental Table 3 (Supplemental Digital Content 3, http://links.lww.com/PCC/B143) for details of quality assessment.

flow nor vessel density was improved upon initiation of veno-arterial extracorporeal membranous oxygenation (ECMO) (53). Neonates who are hypotensive immediately after birth have altered vessel density that does not respond to resuscitation but improves within 12 hours (55). Finally, neonates with congenital diaphragmatic hernia had altered flow and vessel density that did not respond to inotrope therapy (38).

The nine studies relating microcirculatory flow to gender or postnatal age are not discussed because they did not separate cohorts based on diagnosis or disease severity, rendering analysis on those variables impossible (65–73).

DISCUSSION

The vascular system is responsible for the delivery of oxygen and nutrients to cells, a task so critical it has been dubbed "the organ of the intensivist" (74). Despite this significance, our review has revealed a paucity of studies on microcirculatory blood flow in critically ill children, with only 502 patients assessed across 27 studies. The settings of these studies and disease severity of their participants, demonstrate that assessment of microcirculatory function in critically ill children and neonates may be difficult but is possible. Analysis of the collected literature is challenging due to great variability in the patient populations, diagnoses, treatment factors, and assessment timepoints. Despite these limitations, several important conclusions may be drawn on the nature and implications of microcirculatory changes in severely ill children and neonates.

The prevalence of microcirculatory dysfunction in children remains unknown. In adults, more than 15% of intensivve care patients will have dysfunctional microcirculatory flow, and that its presence correlates with mortality (75, 76). Based on the studies we reviewed, microcirculatory irregularities appear to be more prevalent among critically ill pediatric patients despite a broad range of ages and conditions. Gonzalez et al (44) conducted the most comprehensive study of microvascular dysfunction in general PICUs. However, definitive conclusions from this study are difficult to draw due to low enrollment of only 18 eligible children, including the exclusion of multiple critically ill as well as generally well patients. The exact prevalence of microvascular dysfunction and its consequences is not known because studies lacked control groups, as well as the lack of pediatric normative data for microcirculatory variables and low PICU mortality rates (77). More worrisome, multiple studies demonstrated that microcirculatory dysfunction correlated with biochemical markers of tissue perfusion inadequacy, such as lactate and interleukins, but not with macrovascular variables, implying loss of hemodynamic coherence (39, 42, 44). Across similar disease states, several studies of demonstrate more significant microcirculatory dysfunction in children and neonates compared with adults (39, 44), suggesting this may be a more significant problem in younger patients.

The effects of common therapies on microcirculatory dysfunction are more clear. Six studies in children and neonates demonstrated that interventions to normalize macrovascular variables did not correct microvascular flow in the setting of inotropic therapy (39, 57), therapeutic hypothermia (42, 54), and ECMO (53). These findings are especially concerning since patients are considered for such therapies due to inadequate oxygen delivery, yet their application may not correct the underlying microvascular defects. Such differences are likely explained by variations in the device used and timing and location of assessments. In instances of rapid clinical decline, it is difficult to tease out the effects of multiple simultaneous interventions. Many of the studies in neonates used

TABLE 4. Studies of Microvascular Function in Critically Ill Neonates

References	Design	Critically Ill Patients	Control Patients	Method of Assessment	Site of Assessment	Quality Assessment	Major Findings
Pöschl et al (46)	POC	12	21 healthy Seven nonseptic	LDF	Back, thigh, heel skin	Medium	Infants with sepsis have reactive hyperemia compared with controls and changes occur before C-reactive protein or leukocyte count increase
Martin et al (47)	POC	12	20	LDF	Dorsal hand skin	Low	Infants with sepsis have reactive hyperemia (by postocclusive perfusion measurement) that correlates with increased IL-6, IL-8, and tumor necrosis factor compared with controls
Genzel-Boroviczény et al (48)	POC	13	0	OPS	Upper arm skin	Low	Blood transfusion improved FVD in critically ill preterm anemic neonates but did not affect vessel diameter, RBC velocity, or flow
Top et al (49)	POC	14	10	OPS	Buccal mucosa	Medium	FCD is significantly lower in neonates with ARDS before ECMO compared with control patients. FCD increased significantly after ECMO decannulation
Weidlich et al (50)	POC	17	Four	OPS	Upper inner arm skin	Medium	Functional small vessel density declined in infants with infection before laboratory findings
Hiedl et al (51)	POC	13	12	SDF	Inner upper arm skin	Medium	FVD was lower in infants with hemodynamically significant PDA but same as control group after PDA closure
Top et al (52)	POC	Eight	0	OPS	Buccal mucosa	Low	Inhaled nitric oxide improves FCD in the buccal mucosa of infants with hypoxemic ARDS
Top et al (53)	POC	21	Seven	OPS	Buccal mucosa	Medium	FCD increased slightly but MFI and HI did not change after initiation of venoarterial ECMO in neonates with cardiopulmonary failure in comparison to ventilated controls
Ergenekon et al (54)	POC	Seven	Seven	SDF	Axilla skin	Medium	Infants treated with TH had lower MFI and decreased flow velocity that normalized with rewarming
Schwepcke et al (55)	POC	10	11	SDF	Right arm skin	Low	Within the first 6 hr of life, hypotensive infants have higher FVD. FVD did not respond to medical management and normalized by 12 hr after birth

(*Continued*)

TABLE 4. (*Continued*). Studies of Microvascular Function in Critically Ill Neonates

References	Design	Critically Ill Patients	Control Patients	Method of Assessment	Site of Assessment	Quality Assessment	Major Findings
Buijs et al (38)	POC	21	Seven	SDF	Buccal mucosa skin	Low	Infants with congenital diaphragmatic hernia requiring dopamine had lower proportion of perfused vessels and MFI. All microcirculatory variables in hypotensive neonates were lower than normal newborn controls. Inotropes corrected macrovascular but not microvascular indices
Dehaes et al (56)	POC	10	17	Frequency-domain near-infrared spectroscopy, diffuse correlation spectroscopy	Left, middle, and right frontal regions	High	Infants with HIE undergoing TH had a lower cerebral blood flow in comparison to control infants or post-TH
Ishiguro et al (57)	Case report	One	0	LDF	Forehead and foot skin	Low	A neonate in septic shock had decreased skin blood flow and MAP despite inotropes but flow and MAP did increase with blood transfusion
Nussbaum et al (58)	POC	40	15	SDF	Ear conch skin	Medium	Infants undergoing cardiopulmonary bypass had decreased MFI, perfused vessel density, and vessel glycocalyx width. Values were similar to control infants within 24 hr
Fredly et al (59)	POC	28	0	LDPM, CAVM, DRS	Chest skin	Medium	Neonates with HIE and high C-reactive protein have lower FVD compared to infants with HIE and low C-reactive protein. Flow and heterogeneity were not significantly different
Fredly et al (60)	POC	28	25	LDPM, CAVM, DRS	Chest skin	Medium	Infants with HIE undergoing TH had a lower capillary flow velocity and increased FCD, HI, and O_2 extraction. Values were similar to control infants after rewarming
Neunhoeffer et al (61)	POC	20	30	LDF, tissue spectrometry	Placed above both kidneys	Medium	Infants undergoing cardiopulmonary bypass that developed acute kidney injury had decreased renal oxygen saturation and higher renal blood flow and renal resistive indices

(*Continued*)

TABLE 4. (*Continued*). Studies of Microvascular Function in Critically Ill Neonates

References	Design	Critically Ill Patients	Control Patients	Method of Assessment	Site of Assessment	Quality Assessment	Major Findings
Troiani et al (62)	POC	12 ARDS Seven cardiac	28	LDF	Back of forearm skin	Medium	Infants with ARDS had decreased skin microcirculatory flow velocity and reserve compared with infants with cardiac abnormalities or those without ARDS
Puchwein-Schwepcke et al (63)	Randomized clinical trial	Six	Six	SDF	Inner right arm skin	Medium	Infants randomized to high co_2 tension group had reduced FVD and increased medium/large vs small vessel distribution
Neunhoeffer et al (64)	POC	14 hypoplastic left heart syndrome 14 transposition of the great arteries	0	LDF, tissue spectrometry	Right forehead skin	Medium	Relative cerebral blood flow did not change in infants before and after heart surgery requiring cardiopulmonary bypass despite differences in cerebral oxygen extraction

ARDS = acute respiratory distress syndrome, CAVM = computer-assisted video microscopy, DRS = diffuse reflectance spectroscopy, ECMO = extracorporeal membranous oxy0067enation, FCD = functional capillary density, FVD = function vessel density, HI = heterogeneity index, HIE = hypoxic-ischemic encephalopathy, IL = interleukin, LDF = laser Doppler flowmetry, LDPM = laser Doppler perfusion measurement, MAP = mean arterial pressure, MFI = microvascular flow index, OPS = orthogonal polarization spectral imaging, PDA = patent ductus arteriosus, POC = prospective observational cohort study, SDF = side-stream dark field imaging, TH = therapeutic hypothermia.

See Supplemental Table 3 (Supplemental Digital Content 3, http://links.lww.com/PCC/B143) for details of quality assessment.

LDF instead of videomicroscopy, making direct comparisons between patient populations impossible, as in the comparison of inotrope use and blood transfusion with sampling via LDF versus SDF (48, 50). The variable variables assessed and outcome measures render more general conclusions untenable. These results are especially significant given the finding of the recent ANDROMEDA-SHOCK trial showing improved mortality in peripheral perfusion rather than lactate directed resuscitation in adults with septic shock (78). The collected literature indicate that microvascular dysfunction is common and likely underappreciated in the neonatal ICU (NICU) and PICU and may have significant clinical consequences and treatment implications.

Few studies provide some insight into the effects of various therapies on the microcirculation. In neonates with respiratory distress syndrome, the application of inhaled nitric oxide improved PVD (52). Well known for its pulmonary vasodilatory effects, nitric oxide has multiple extra-pulmonary actions (79). In the only randomized control trial identified, permissive hypercapnia, a therapeutic approach commonly used in neonatal respiratory distress syndrome, was shown to decrease vessel density (63). Similarly, neonates with congenital diaphragmatic hernia, treated with dopamine to correct HR and BP, continued to have reduced flow and vessel density (38). These findings have important clinical relevance since inotropic infusions commonly applied to treat shock may, in some instances, compromise end-organ tissue perfusion. Defining how the microcirculation changes respond to common therapies and the ultimate impact on tissue perfusion and outcomes is an urgent research priority.

There are limitations to this investigation. As we have noted, there are multiple methods to assess the microcirculation that are not directly comparable. Standardization of techniques and measurements, as well an agreement on age-specific normal values, are essential to advancing our understanding of microvascular function. Without standard normal ranges for specific ages, body sizes, and genders, the work done to assess the microcirculatory flow at the capillary level is not generalizable to the NICU and PICU settings. More trials with greater subject numbers are needed to validate a method, timing, and location of assessment. The limited number of studies, low quality of evidence, and diagnostic and methodologic heterogeneity precluded a quantitative meta-analysis. Our review may further be limited by the potential impact of publication bias, as studies not finding a correlation between critical illness and disruption of microvascular flow are less likely to be published. Although we attempted to identify all relevant studies, it is possible that qualifying studies were inadvertently omitted from this systematic review. Despite these challenges, we felt it was important to try to understand the range of clinical settings in which microvascular monitoring is feasible and potentially informative. In fact, technology has sufficiently advanced to allow clinical researchers to begin to explore how patient and treatment factors alter the microcirculation of our patients. Multiple ongoing studies aim to address some of these concerns.

CONCLUSIONS

Adequate microvascular blood flow is essential for the maintenance of cells and organ function. Homeostasis relies on hemodynamic coherence, where microcirculatory flow is mirrored by macrovascular variables. Despite logistic challenges, microvascular flow may be measured with LDF or videomicroscopy. In critically ill children, microvascular blood flow may be disrupted, and hemodynamic coherence may be lost. The timing, severity, and clinical consequences of these changes are not well defined. More research is required to better understand how microvascular variables can be monitored in critically ill children, define age-appropriate normal values, assess responses to common interventions and ultimately, define its impact on PICU morbidity and mortality.

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