Reconsidering Vasopressors for Cardiogenic Shock

Everything Should Be Made as Simple as Possible, but Not Simpler

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Scientific statements and publications have recommended the use of vasoconstrictors as the first-line pharmacologic choice for most cases of cardiogenic shock (CS), without the abundance of strong clinical evidence. One challenge of guidelines is that the way recommendations are stated can potentially lead to oversimplification of complex situations. Except for acute coronary syndrome with CS, in which maintenance of coronary perfusion pressure seems logical prior to revascularization, physiologic consequences of increasing afterload by use of vasoconstrictors should be analyzed. Changing the CS conceptual frame, emphasizing inflammation and other vasodilating consequences of prolonged CS, mixes causes and consequences. Moreover, the considerable interpatient differences regarding the initial cause of CS and subsequent consequences on both macro- and microcirculation, argue for a dynamic, step-by-step, personalized therapeutic strategy. In CS, vasoconstrictors should be used only after a reasoning process, a review of other possible options, and then should be titrated to reach a reasonable pressure target, while checking cardiac output and organ perfusion.

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Cardiogenic shock (CS) is a low cardiac output (CO) state due to heart failure, resulting in life-threatening end-organ hypoperfusion and hypoxia.[1,2] In the setting of acute myocardial infarction, support of coronary perfusion pressure with vasoconstrictor agents as an initial step prior to revascularization seems reasonable. CS, however, occurs in many other settings, including decompensation of chronic heart failure, fulminant myocarditis, post-cardiac arrest, severe valvular heart disease, right ventricular failure, and as a component of mixed shock in lung injury, sepsis, and other inflammatory conditions. In these settings, application of an early vasoconstricting approach intended for BP support may not always be the best course of action.

In the classic pathophysiologic model of CS, early compensatory systemic vasoconstriction occurs in order to maintain BP and organ perfusion. Persistence of tissue hypoxia, however, may induce inflammation with subsequent altered vasoreactivity,[3]

ABBREVIATIONS: CO = cardiac output; CP = cardiac power; CS = cardiogenic shock; Ea = arterial elastance; LV = left ventricle; RV = right ventricle; V_{O_2} = oxygen consumption

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which can change the paradigm.[4] Consequently, the choice of pharmacologic treatment may change from pure inotrope or inodilator support[5,6] to a combination of inotropes and vasoconstrictors.[1,7,8] Although comparative studies combining different drug strategies are lacking, several scientific societies have recommended in high-impact journals that drugs with a predominantly vasoconstrictive effect—mostly norepinephrine—be used alone as the first-line treatment,[2,9] eventually associated with inotropes when the low-flow state persists. Although cautiously written, these recommendations tend to prioritize pressure over flow, which may initially improve BP, but present a risk of potential deterioration thereafter.

Although simple messages for early management are desirable, there is a risk that oversimplification may lead to suboptimal treatment that can affect outcome. The CS context is very heterogeneous in many aspects, in part because a delay from the onset of acute hemodynamic disorders to initiation of treatment can change the clinical presentation. Thus, even if a "one-size-fits-all" approach may be logical early on, and may lead to a statistical improvement in a large population, it cannot be safely generalized to all situations and does not guarantee an optimal strategy on an individual basis.

This review aims to summarize the conceptual, pathophysiologic, and therapeutic evidence arguing for a more dynamic, granular, and personalized approach, and to suggest an algorithmic process based on well-established priorities.

Conceptual Viewpoint

The recommendation for using vasoconstrictors as the first choice in CS ultimately rests on a concept that prioritizes pressure over flow, essentially treating the consequences of cardiac dysfunction (hypotension) as opposed to constructing a conceptual model based on the causes of cardiac dysfunction.[1,2] An approach based on BP seems to support symptomatic treatment more than interventions focused on mechanisms that have been understood and modeled. While the initial goal in CS is to support coronary and organ perfusion pressure, the mechanisms mediating the circulatory disorder may differ in different settings. We propose a broader conceptual model that considers tissue and coronary perfusion as a function primarily of low cardiac output, but with variable contributions from hypoxia, endothelial dysfunction, inflammation, and vasoplegia (Fig 1). The interplay of different factors results in a complex association of causes and consequences that may or may not respond adequately to vasoconstrictors.

As recommendations for initial support are necessary, they should be supplemented by detailed bundles that take into account the evolution of the shock syndrome,

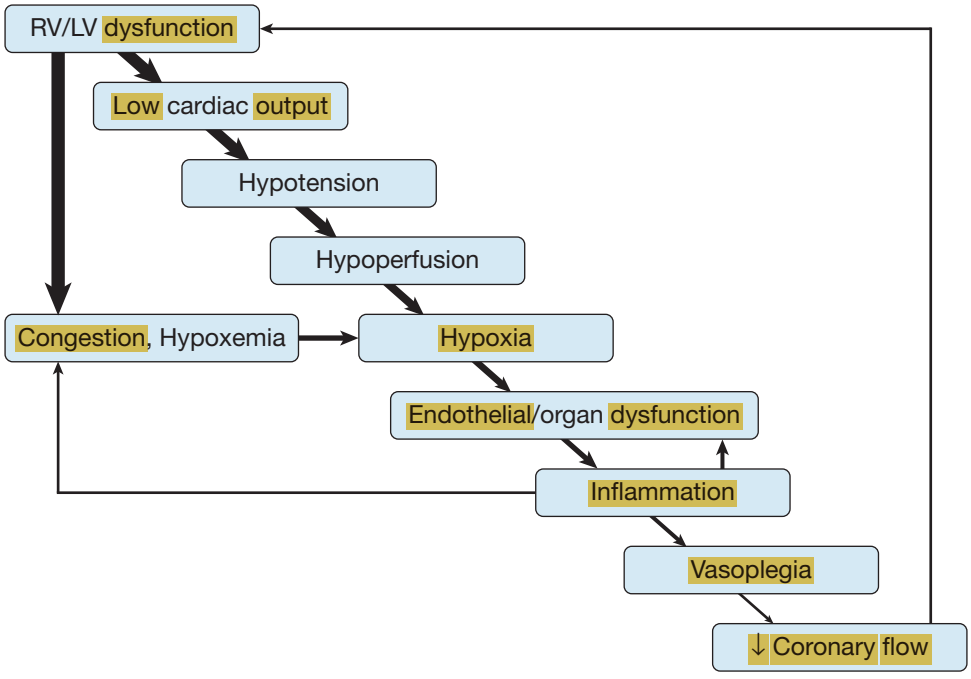

Figure 1 – *Cardiogenic shock downward cascade. The thickness of the arrows schematically represents the strength of the linkage depending on the severity and duration of the disorder and on the patient's physiologic reserve. LV = left ventricle; RV = right ventricle.*

integrating a comprehensive pathophysiologic model, as has been done with septic shock.[10] Since knowledge comes in successive layers that encompass previous concepts,[11] the new insights and developments in CS pathophysiology do not invalidate the past studies. A decrease in CO associated with organ congestion and hypoperfusion remains the landmark characteristic of CS, seen in combination with symptoms of acute heart failure and shock.[12,13] Without clear distinction between causes, consequences, time between them, and without CO and tissue perfusion assessment, replacement of the classic mechanistic model based on hemodynamic subsets[14] by a phenotypic classification based on BP[2] is not an advance in the level of knowledge.

Pathophysiology

The Cardiogenic "Clock" Time

CS is a syndrome with a conventional definition for which the key concept is shock, a circulatory disorder leading to a severe imbalance between oxygen needs and oxygen consumption (Vo_2).[15] All Vo_2 components are interrelated to maintain Vo_2 close to the oxygen needs. When a component is failing, others are stimulated to compensate.[16] Moreover, an adaptation, called the "conformance phenomenon," may reduce oxygen needs when oxygen delivery decreases.[17] All these mechanisms are overwhelmed when shock occurs and the oxygen deficit increases with time. As a result, both macro- and microcirculations are modified, with mutual interactions.

In the early phase, the microcirculation and macrocirculation are coherently linked, but it was shown that, very rapidly, a significant proportion of patients may have incoherence between the two, with persistent tissue hypoperfusion despite improvement in macrocirculation.[18] This can be caused by heterogeneities in the microcirculation, decrease in the capillary density, local reduction of flow, or tissue edema, and may lead to irreversible damage.

After time, in any shock state the symptoms can be dominated in different proportion by the systemic inflammatory response, adding complexity to the initial event.[4,19] As a consequence, the compensatory mechanisms to fit with oxygen needs may be less efficient, with various alterations in myocardial contraction,[20] lung function, microcirculation, and organ function.[21,22] On top of these alterations, the response to vasoactive mediators and drugs can be severely altered.[23] On an individual basis, there is considerable heterogeneity in inflammatory response depending on individual susceptibility according to age, comorbidities, genetic factors, chronic treatment, and organ damage.[24,25] The tissue response to CS status is also influenced by the etiology and severity of shock and the delay between the onset of shock and the initiation of treatment.[26] The response to stress finally includes a metabolic component with hyperglycemia,[27] metabolic acidosis, and tissue hypercapnia, adding to the complexity of the observed symptoms.[28] All interactions and combined heterogeneities suggest an interplay between the initial circulatory disorders and the subsequent consequences that may vary largely among individuals. Inflammation-induced cell function alterations and metabolic shift may lead to irreversible damage and cell death with organ failure.

In the terminal phase of shock, characterized by multiple organ failure, it becomes difficult to separate the different mechanisms responsible for the poor response to a hemodynamic treatment.[29,30] Hence, the delay between onset of shock and therapy is a major determinant of the clinical presentation and of the reversibility of organ failure.

The Hemodynamic Aspects

Mechanistically, the circulation is a closed-loop system with a double power generator: the right (RV) and left (LV) ventricles, with components both in series and in parallel. This approach is not simply theoretical, because it allowed the development of efficient in silico circulatory models,[31,32] commonly used for teaching and for designing and testing artificial hearts, prosthetic valves, and noninvasive technologies for CO assessment. Therefore, as a first approach, it is reasonable to see CS as a pump dysfunction with forward and backward consequences rather than as an array of phenotypic presentations.

Pump dysfunction: The resistance to flow is traditionally estimated at the bedside by using a transposition of Ohm's law (pressure = flow × resistance), and assuming continuous pressure and flow. This basic approach does not allow analysis of how the mechanical energy of the cardiac contraction is transformed into hydraulic energy (flow). Intuitively, it can be easily understood that the ventricle ejection would be harder if the arterial system was rigid (fixed vascular size and vasomotor tone), as compared with elastic. The analysis of the phasic interactions between two chambers with elastic properties was named *ventriculoarterial coupling* by Sunagawa et al,[33] and

requires models in the frequency domain. Any decrease in the ventricle afterload is likely to improve the ventriculoarterial coupling.[34] The ventricle afterload is therefore best evaluated by the arterial total impedance,[35] the equivalent of a time-varying resistance, whose main components are the arterial elastance (Ea) and the systemic vascular resistance.

It has been long recognized that increasing ventricular afterload induces a rapid decrease in stroke volume when systolic ventricular function is severely limited (Fig 2).[36,37] If the maintenance of coronary perfusion pressure is always a major goal during CS, a reduction in afterload may improve ventricular ejection[38,39] and potentially reduce myocardial ischemia and organ hypoperfusion. In both RV[40] and LV failure,[41] a decrease in ventricular afterload has been proposed as the first line of treatment. Reduction of both systemic vascular resistance and Ea combined with potentially improved systolic ventricular function leads to a modest, and most often acceptable, BP decrease. This was also the rationale for developing inodilators such as milrinone and levosimendan.[42]

When vasoconstrictors such as norepinephrine are used, they modify the contraction efficiency and consequently, the myocardial energetic needs, as illustrated by the ventricular pressure/volume loops and areas (Fig 3).[43] An increase in afterload (rightward shift of the Ea slope) decreases stroke volume and ventricular efficiency. This can theoretically be compensated by a proportional leftward shift of the ventricle elastance slope, which supposes a direct or indirect inotropic effect. This effect has been demonstrated with norepinephrine in animal models[44] and in isolated human tissue.[45] The absence of an increase in heart rate after norepinephrine infusion

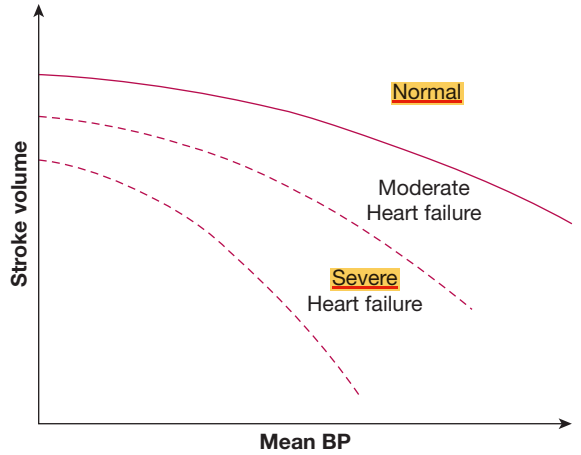

Figure 2 – *Stroke volume and BP relationships in the normal and failing heart. (Adapted with permission from Weber et al.[37])*

suggests a modest clinical inotropic effect, but one that is usually less pronounced than the increased afterload effect.[46] Moreover, its inotropic effect is unpredictable,[47] and seems to decrease in failing hearts.[48] In a recent study, norepinephrine did not increase CO within the first 12 hours of infusion in CS after myocardial infarction.[49] In any case, even though an inotropic effect may help maintain stroke volume when a failing ventricle faces an increased afterload, the upward shift of end-systole increases the total workload and therefore the myocardial oxygen needs. In contrast, a reduction in afterload may improve cardiac reserve and ventricular metabolism. Moreover, when the LV fails, the RV afterload is increased. Since the RV is a "volume pump" and not a "pressure pump," it does not tolerate acute increases in afterload well. Hypoxic pulmonary vasoconstriction and acute systemic inflammation can further exacerbate increases in RV afterload, as can treatment with norepinephrine.[50] Biventricular failure can cause global hemodynamic degradation, combining hypoperfusion and venous congestion.

The cardiac power (CP = CO × mean BP) is consensually seen as the best simple prognostic indicator of compensated or decompensated cardiomyopathy, with or without CS.[51,52] This indicates that any failing heart has a rather limited and invariant CP depending on myocardial oxygen delivery and global (biochemical and mechanical) heart pump efficiency. For any predetermined level of CP, increasing BP necessarily decreases CO, unless the increase in BP improves either insufficient coronary flow or heart pump efficiency (therefore CP). Insufficient coronary flow may increase when driving pressure (aortic pressure – intracardiac pressure) is augmented, improving the myocardial energetic balance. Such improvement can be obtained by an increase in BP, a decrease in intraventricular pressure, or both. For the RV, because coronary perfusion is normally present during the whole cardiac cycle, coronary blood flow depends on both systolic and diastolic perfusion pressure. In cases of severe pulmonary hypertension, RV coronary perfusion occurs predominantly in diastole, as occurs in the LV. Augmentation of aortic pressure with a vasopressor may improve RV coronary perfusion, if arterial BP increases more than pulmonary pressure and if end-diastolic RV pressure does not rise proportionally.[53]

Theoretically, increasing the myocardial efficiency by increasing afterload is also possible (Fig 4).[44] However, in the failing heart, the optimal afterload is narrow and must be tuned carefully, which mandates hemodynamic

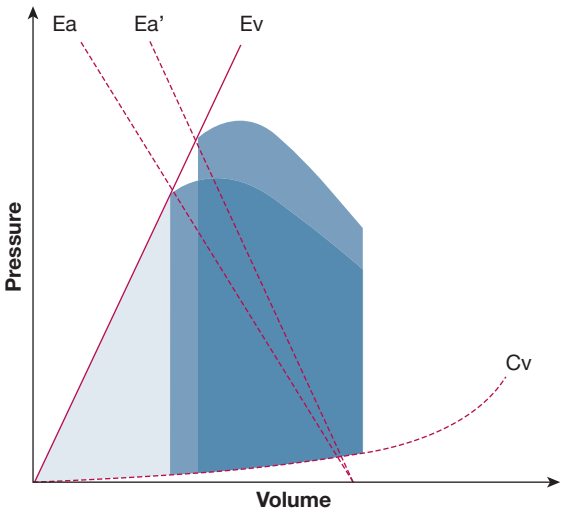

Figure 3 – *LV schematic pressure and volume relationship. Cv = ventricle compliance, Ev = ventricular elastance, Ea = arterial elastance, reported on the ventricle loop by inverting the volume axis, as originally described by Suga.*[43] *The intersection between Ea and Ev indicates end systole. The dark blue area inside the loop represents the external work. The light blue area (triangle formed by the Ea slope, the Cv curve, and the leftward line of the ventricle loop) represents the potential energy, lost during relaxation. The sum of the external work and the potential energy is the total energy and determines myocardial oxygen consumption. The ratio between external work and total energy can be seen as an index of ventricle mechanical efficiency. An increase in afterload schematized by a rightward shift of Ea (Ea′) leads to a change in all myocardial energetic values. Although of different shape, the RV loop has the same characteristics. See Figure 1 legend for expansion of other abbreviations.*

assessment with continuous and independent BP and CO measurements.

Forward consequences: Reduced CP leads to immediate heterogeneous tissue perfusion, with preferential flow regulation mediated by the vascular tone. The myocardium, brain, kidneys, and liver have protective autoregulation mechanisms (Fig 5).[54,55] In other organs—targets of stimulated baroreflexes and endocrine mediators such as catecholamines, vasopressin, and angiotensin—the regional blood flow is redistributed, as can be seen by the physician (mottling and cold skin).[56] Tissue hypoxia and inflammation may change tissue autoregulatory capabilities,[22,57] with unknown consequences on the pressure/flow relationship of vasopressors,[58,59] which justifies the concept of functional hemodynamics.[60] In addition, vasopressors such as norepinephrine modulate immune function in a context-dependent manner, with a risk of increasing inflammation.[61,62] Furthermore, treatment-induced vasoconstriction of already vasoconstricted territories may further jeopardize their perfusion and lead to severe ischemia.[63] Because of all of the above arguments, the systematic use of vasopressors to restore adequate perfusion in different tissues may be hazardous in the absence of a more solid understanding of the underlying hemodynamics and tissue perfusion.[59,64]

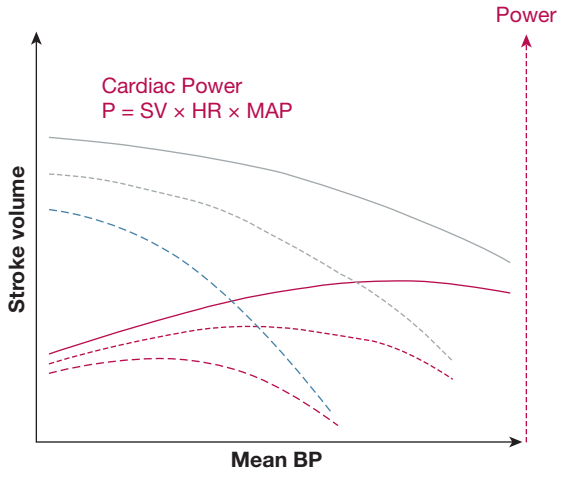

Figure 4 – *Cardiac power, considering the same stroke volume and BP values as in Figure 1 and a fixed heart rate. Power curves are in red with corresponding plain or dotted lines. HR = heart rate; MAP = mean arterial pressure; SV = stroke volume.*

Backward consequences: The backward consequences of CS for both LV and RV lead to symptoms primarily related to "venous congestion." The driving pressure for venous return to the RV is low (around 5 mm Hg) because of low venous resistance, but has to be maintained in RV congestion by a proportionate increase in venous pressure. An acute rise in right atrial pressure to 15 mm Hg in CS requires a tissue venous

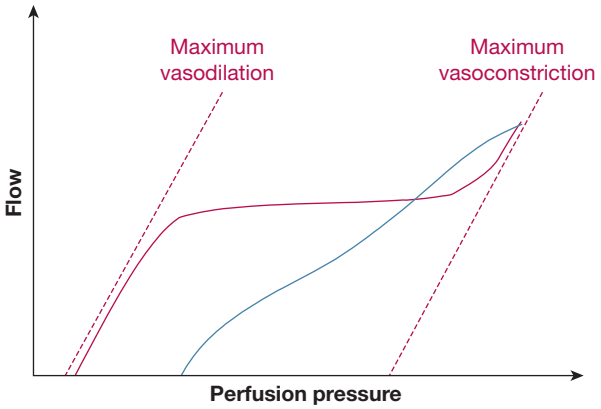

Figure 5 – *Pressure-flow relationships. The x axis denotes the organ perfusion pressure. The y axis is the scale for organ flow. The dotted lines show the linear pressure/flow relationships in tissues with no autoregulation (skin, muscles, gut, and lungs). The scale of values on the x and y axes (and therefore the slopes showing the vascular tone) are specific for each tissue. Autoregulation of flow results from the ability of the arteries to change their tone (caliber) when perfusion pressure changes within limits to maintain constant flow. In red, the curve in autoregulated organs such as heart or brain.*[54] *In blue, the pressure-flow relationship of the kidney and liver, with more limited autoregulatory capabilities.*[55]

pressure close to 20 mm Hg to maintain venous return. This backpressure in organs may largely impair their perfusion by reducing the perfusion pressure gradient (systemic artery pressure – venous organ pressure).[65] The rheologic and ischemic consequences are of particular importance in organs with no antireflux venous valves, and those perfused both in systole and diastole, such as the brain, the RV, and the kidneys. If diastolic perfusion pressure is reduced to 30 mm Hg or less, this value becomes insufficient to overcome the intraorgan resistance, especially when the organs are surrounded by a nonextensible serosa. This noncompliant serosa limits the volume expansion of the organ, increasing the interstitial pressure and compressing vessels. Moreover, norepinephrine-induced increase in hydrostatic pressure,[66] associated with a capillary leak, may increase the filtration and interstitial edema,[67] as observed in lung tissue when venous congestion is present. Finally, the effects of vasoconstrictors on tissue perfusion pressure can be unpredictable, with differential effects on arterioles and venules,[59,66] especially if inflammation is present.

The tissue consequences: At the tissue level, the circulation has a dual function: supply of oxygen and nutrients from blood vessels and transporting waste products in the blood, such as carbon dioxide. This vital process, investigated over several centuries, has been computed for simulation training.[68] Whole body oxygen delivery is the product of CO × arterial oxygen content. Oxygen consumption is the product of CO × the arteriovenous difference in oxygen content. Therefore, if a minimum BP is necessary to perfuse the tissue, as seen in Figure 5, the key variable for mass transport is always flow. This is even more complex at the microcirculation level, but it seems reasonable to prioritize flow improvement. Increasing BP above a critical threshold has not been proven to be effective; studies in ICU patients failed to show any benefit (survival rate or organ failure) when increasing arterial pressure using vasoconstrictors.[69,70]

Therapy

Shock is a therapeutic emergency, a situation in which oxygen delivery fails to keep up with metabolic needs. Given this imbalance, therapy to reduce tissue metabolism might be considered early on, potentially including control of hyperthermia and sedation to decrease muscle and brain oxygen utilization.[15,71] On the other hand, optimization of oxygen delivery could include correcting anemia, increasing oxygen saturation, improving tissue extraction (by improving microcirculation and reducing microclotting, inflammation, and tissue edema), and finally improving the heart pump function.

Since the heart consists of two pumps connected in series, both RV and LV function have to be improved.[32,72] Recommendations in the treatment of acute and chronic heart failure sequentially include the following[73,74]: reduction of ventricular afterload (therefore increasing CO and reducing myocardial oxygen needs), optimization of preload (increasing CO without change in myocardial oxygen needs), and consideration of use of inotropes (increasing both CO and myocardial oxygen needs). Last, vasopressors can increase BP, but typically at a cost of decreased CO and increased myocardial oxygen needs. Accordingly, the use of vasodilators at any stage of compensated or decompensated heart failure is beneficial, based on existing evidence.[13,74]

A vasoconstrictor strategy for CS treatment promotes an approach based on BP, which, while important, does not necessarily reflect CO or tissue perfusion.[64,75] The important interpatient variability may preclude application of a rigid oversimplified therapeutic scheme. Vasopressors can be employed as an emergency treatment, but this can rapidly be modified on the basis of a personalized therapeutic strategy.[76] In some patients and at some times in the clinical course, vasodilators may have more beneficial effects on tissue perfusion, even transiently. Given this complexity, a structured approach, considering oxygen utilization, ventricular function, CO, BP, and tissue perfusion, should be recommended. Basically, surrogate measures of tissue hypoperfusion include an increase in plasma lactate concentration, an increase in arteriovenous carbon dioxide gradient, a drop in skin temperature, and low capillary refill time. However, the microcirculation can be more directly investigated using cutaneous laser Doppler, muscular oxygen saturation by near-infrared spectroscopy, or hand-held video microscopy allowing one to assess the changes in microcirculatory blood flow, tissue oxygenation, and functional capillary density.[77]

The treatment of CS must be a compromise between the best tissue perfusion possible and the lowest myocardial energy cost.[12] A complete algorithmic approach has been created and validated but requires thousands of lines of code.[78] Figure 6 summarizes the potential flow-based approach as discussed above. The emergency strategy of care should integrate the different items, considering "the faster the better" for patients' outcome. This implies rationalizing the strategy in light of comorbidities and chronic treatments, and choosing to

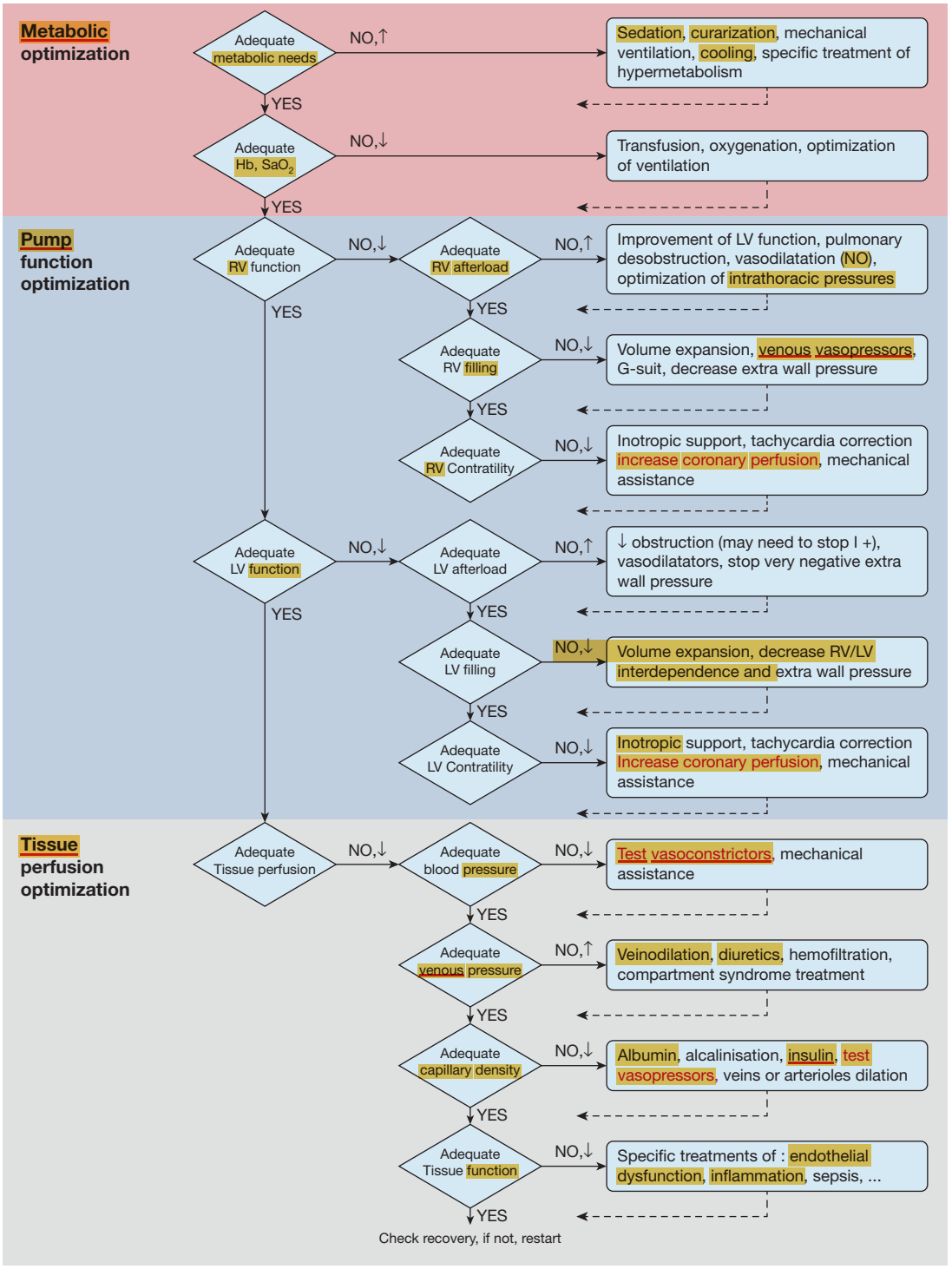

Figure 6 – *Cardiogenic shock schematic strategy of care. On the left, the diamonds indicate a question and, on the right, the rectangles indicate an action to be considered. Only the most likely actions are listed in this schematic representation. The dashed arrows indicate the need for a revaluation after action, therefore going back to the previous question (diamond). In all questions, "adequate" does not mean "statistically normal" but that the variable (or function performance) is low or high enough to contribute appropriately to the organ perfusion and that the patient would not benefit a priori from a manipulation of that variable. The steps that mandate consideration of vasopressors are reported in red. Initial emergency interventions such as resuscitation, extracorporeal life support, cardiac surgery, pericardial and pleural drainage, coronary reperfusion, cardioversion, and pacing are not included in this scheme. Hb = hemoglobin; NO = nitric oxide; Sa_{O_2} = arterial oxygen saturation. See Figure 1 legend for expansion of other abbreviation.*

omit steps with poor potential benefit in some patients. If vasoconstrictors must be used, it should be only after a reasoning process considering other options, and titrated to reach a reasonable pressure target, while checking CO and organ perfusion.[76] Optimization of CO and perfusion may include the use of different drugs with various effects, combining more or less vasoactive and inotropic properties, as summarized in the American Heart Association statement.[2] The best choice depends on the specific patient's balance between CO, BP, and tissue perfusion and on the potential risks, especially considering the heart rate, coronary reserve, and presence of severe arteriosclerosis. This type of personalized therapy based on a step-by-step analysis of the determinants of organ perfusion has been shown to reduce length of stay in selective populations with CS.[79] In other types of shock, rapid hemodynamic stabilization based on oxygenation targets or lactate clearance has also increased survival.[29,80] However, there is no clinical evidence showing the superiority of a flow-directed approach relative to a pressure-based strategy. This review is a plea for a comparative study.

Conclusion

CS is an example of a complex situation in which validated physiologic models should structure clinical reasoning. Current paradigms with excessive reliance on systematic first-line vasopressor treatment do not fully take into account all of the convergent evidence concerning myocardial supply/demand imbalance and tissue perfusion. This simple approach in CS might be too simple in many patients, and might be tested against a stepwise, dynamic, and functional approach, including macro- and microcirculatory assessment.

Acknowledgments

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