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Diastolic arterial pressure is important in septic shock: PRO

Along with heart rate, the arterial blood pressure is the most commonly used variable to assess the cardiovascular status in the general population. Physicians caring patients with chronic hypertension are well aware of the necessity to target a very tight safe range of diastolic arterial pressure (DAP), when using anti-hypertensive drugs [1]. By contrast, the DAP is often underused by intensivists in spite of the simplicity of its measurement. The existence of the current debate is one of the proofs that intensivists often neglect the importance of this variable to manage critically ill patients. This could be in part due to the fact that the systolic arterial pressure and/or the mean arterial pressure (MAP) but not the DAP, are often considered for the definition of shock states. Nevertheless, for at least the two following physiologic reasons, we strongly believe that the DAP should also be taken into consideration in patients with shock: DAP is a good marker of arterial tone and DAP is the upstream pressure for the perfusion of the left ventricle.

Physiologically, a low DAP can be essentially due to depression of arterial tone, bradycardia, or arterial stiffness. In critically ill patients, the main determinant of a low DAP (<50 mmHg) is depressed arterial tone. Indeed, bradycardia is not common and isolated arterial stiffness (more often associated with a large pulse pressure) cannot be responsible for very low DAP values such as those encountered in severe vasodilatory shock states. Tachycardia should theoretically result in a higher than normal DAP as the reduced diastolic time prevents the diastolic decline of the arterial blood pressure to be completed. In general, vasodilatory shock states are associated with both decreased arterial tone and tachycardia, which thus exert opposite effects on DAP. Therefore, in cases of tachycardia, a value of DAP <40 mmHg is strongly suggestive of a markedly depressed arterial tone and should prompt initiation of a vasopressor, as recommended in the 2012 version of the Surviving Sepsis Campaign (SSC) guidelines [1]. Inexplicably, the mention of using DAP to decide to initiate a vasopressor - norepinephrine in practice - has been forgotten in the most recent version of the SSC guidelines [2]. As basic physiology has not changed over the past years, it should be just an oversight!

Another fundamental physiological characteristic of DAP is to represent the upstream pressure for the perfusion of the left ventricle. Indeed, the left ventricle is perfused during the diastole only and not during the whole cardiac cycle, as it is the case for the right ventricle. Therefore, when the DAP is low, as it is frequently the case in early septic shock due to arterial tone depression, there is an increased risk of myocardial ischemia. This risk should be higher in patients with prior coronary artery disease (CAD) as the perfusion pressure is far lower downstream to the coronary artery stenosis compared to upstream. The risk of myocardial ischemia is often underestimated by intensivists due to a common thought that septic shock is associated with normal or high coronary blood flow, even in the cases of septic myocardial depression [3,4]. In fact, studies suggesting such features, investigated coronary blood flow after catheterization of the coronary sinus in hemodynamically stabilized septic patients without prior CAD [3,4]. For example, in the study by Dhainaut et al. [4], the MAP was 66 mmHg on average, so that presumably the DAP was not as low as it is observed in the early phase of resuscitation. Interestingly, the lowest values of coronary blood flow were measured in the patients with a MAP <50 mmHg, and thus presumably with a very low DAP. Moreover, myocardial hypoxia, which was defined by a decreased lactate uptake in the myocardium was present in patients with the lowest coronary blood flow values and thus with the lowest DAP values [4]. Therefore, this study, which is known as the one that suggested that coronary blood flow is normal or higher than normal in hemodynamically stabilized patients with septic shock [4], also clearly showed that myocardial ischemia may occur when the coronary perfusion pressure is low, even in the absence of CAD. In addition, sepsis is associated with endothelial dysfunction and alteration of the microcirculation that may also affect the myocardium. In a study including 70 patients with septic shock with preserved left ventricular ejection fraction, the coronary flow blood reserve of the left anterior descending artery was assessed after adenosine infusion using transesophageal Doppler echocardiography [5]. More than half of the patients had evidence of a reduced coronary flow blood reserve [5]. It was hypothesized that endothelial dysfunction was responsible for the reduction of the capacity of the coronary microcirculation to dilate in response to adenosine [5]. It can be thus expected that a low left coronary perfusion pressure results in development or worsening of myocardial ischemia, even in cases of normal blood flow in the large coronary vessels. In patients with septic shock, increased troponin levels have been associated with left ventricular dysfunction [6]. Although increased troponin level is a marker of myocardial injury of any origin and not only of ischemic origin, it is hard to exclude any harmful effect of low DAP on the occurrence of myocardial injury. In the cardiology literature, there is convincing evidence of the importance of DAP on patient's outcome. In hypertensive patients, lowering pressure targets to <140/90 mmHg causes harm when the DAP is below a certain threshold [7-9]. According to the J-shaped relationship between DAP and outcome variables [9], there is an optimal range of DAP to be reached. In an observational study, Vidal-Petiot et al. analyzed data from 22,672 stable patients with CAD treated for chronic hypertension [10]. The authors showed that DAP values <70 mmHg as well as DAP values ≥80 mmHg were associated with an increased risk of cardiovascular events, cardiac cause of death and all-cause death [10]. A further analysis showed that the J-shaped relationship between DAP and outcome persisted in patients with pulse pressure in the lowest-risk range [11]. This suggests an association between

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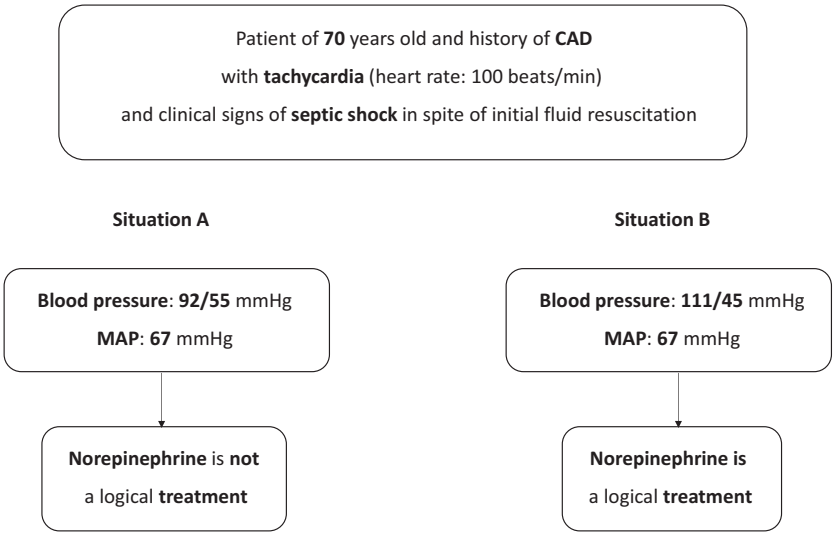

Fig. 1. Here is an illustration that the diastolic arterial pressure (DAP) provides additional information to that of the mean arterial pressure (MAP) in a patient of 70 years old with history of coronary artery disease (CAD) presenting clinical signs of septic shock and tachycardia. In the situation A, blood pressure is 92/55 mmHg, there is no urgency to administer norepinephrine since the MAP (67 mmHg) is above 65 mmHg and the DAP value (55 mmHg) suggests that arterial tone is moderately reduced and that the risk of myocardial ischemia is not high enough. By contrast, in the situation B, the MAP is exactly the same but the low DAP (45 mmHg) suggests that the arterial tone is far lower than in the situation A. Due to the risks of myocardial ischemia in this patient with history of CAD, it is urgent to increase the DAP by administering norepinephrine.

low DAP and compromised myocardial perfusion, independently of increased pulse pressure, which itself represents a cardiovascular risk marker in patients with stiff large arteries. An increased risk of cardiovascular events below a certain DAP level was also described in other high-risk populations, such as patients with a previous cardiovascular event or with diabetes [12]. It can be reasonably hypothesized that such findings could be extrapolated to patients with septic shock as a large proportion of them have a history of chronic hypertension, diabetes and CAD. Therefore, it seems to us important to maintain the DAP above a certain level in septic shock patients in order to avoid an abrupt fall in the left ventricular perfusion and ultimately the occurrence of myocardial ischemia. In this regard, Benchekroune et al. [13] reported in 68 septic shock patients that a value of DAP >50 mmHg was a more powerful predictor of in-hospital survival when compared to systolic arterial blood pressure, to SAPS II score or to the dose of norepinephrine.

We are aware that no randomized controlled trial investigated whether initiating norepinephrine on the basis of a low DAP is associated with a better outcome than initiating it without taking DAP into account. Nevertheless, even in the absence of definitive evidence, clinicians need to make urgent therapeutic decisions in terms of initiation of norepinephrine in patients with shock. Such decisions should logically include basic physiology and individual patient's characteristics. Undoubtedly, knowledge of the DAP can help clinicians in the decision-making process by providing additional information to that provided by the MAP (Fig. 1).

Doubts about the accuracy of the DAP might be raised when obtained with an oscillometric non-invasive blood pressure device. Indeed, such a device does not measure directly the DAP but only estimates it from measurements of the MAP using proprietary algorithms [14]. However, in patients with septic shock, it is recommended to insert an arterial catheter [15,16], which enables direct measurements of the DAP.

To conclude, we believe that the DAP as a marker of arterial tone and as the upstream pressure for the left ventricular perfusion, is as an important variable to be considered in patients with septic shock. Since the DAP is easily obtained in such patients using an arterial catheter, it would be regrettable not to consider it, in particular to identify situations of low arterial tone, where initiation of a vasopressor may be urgent.

Conflict of interest

JLT is a member of the Medical advisory board of Pulsion/Getinge. OH has no conflict of interest to declare.

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Diastolic arterial pressure is important in septic shock: CON

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ABSTRACT

Based primarily on the rational that adequate diastolic pressure is needed to maintain sufficient coronary blood for myocardial needs, diastolic pressure has been proposed as a treatment target for patients in shock. To date, clinical evidence supporting this is limited to observational data. Key points are that what is important for tissues is flow not pressure; the coronary circulation has very large flow reserves and can maintain flow with a low pressure; raising arterial pressure by only increasing vascular resistance does not alter tissue perfusion and could even increase myocardial oxygen demand. Targeting diastolic pressure can lead to over use of vasopressors, which studies have associated with worse outcome. Pressor management in shock should include assessment of indicators of tissue perfusion and changes in flow if possible.

Arterial diastolic pressure has been proposed as a treatment target for the management of patients in shock [1,2]. The potential importance of diastolic pressure is essentially about the heart and not other tissues. The rational is that left ventricular blood flow is impeded during systole; thus, blood flow to the left heart is very dependent upon diastolic pressure [3,4]. If diastolic pressure is too low, coronary perfusion will be inadequate and the left ventricle will become ischemic. The subendocardium of the left ventricle is particularly vulnerable to deficiencies in diastolic blood flow [3] as expressed in variations of the concept of the myocardial oxygen-supply demand index. These relate pressure-time in diastole, an indicator of the oxygen supply to the heart, and the pressure-time in systole, an indicator of myocardial oxygen demand [3].

The clinical importance of diastolic pressure was studied first in the context of cardiopulmonary resuscitation. In animals, a diastolic pressure of ≥30 mmHg improved return of spontaneous circulation during sustained cardiac arrest (CPR) [5]. It subsequently was argued that coronary perfusion pressure is more important than just diastolic pressure. In a prospective observational study in humans undergoing CPR for cardiac arrest, it was shown that a coronary perfusion pressure of ≥15 mmHg was more important than diastolic pressure [6].

A retrospective study of women with severe post-partum hemorrhagic shock raised the potential importance of diastolic pressure in shock [7]. The study objective was to determine if the drugs used to reduce post-partum bleeding caused myocardial injury as assessed primarily by a rise in troponin. No harm was related to the drugs, but a systolic pressure <80 mmHg or diastolic pressure <50 mmHg were associated with a rise in troponin. These patients also had more frequent ECG changes suggestive of ischemia and decreased left ventricular function. In most of patients the troponin concentration fell in 24 h or less and ventricular function quickly improved.

The same investigators later performed a prospective observational study of patients with septic shock to determine if the evolution of cardiovascular reactivity is a better predictor of in-hospital survival than organ dysfunction scores [8]. Two factors were associated with survival: continuous restoration of vascular tone by use of <0.5 μg/kg of norepinephrine and a diastolic pressure >50 mmHg on day 3. The unusual study design makes the interpretation of this data difficult. Patients only were included if they did not receive norepinephrine in the first 24 h of admission, and subjects had to remain on vasopressors for least 72 h. Non-survivors received higher doses of norepinephrine consistent with more refractory shock. Besides the obvious selection biases, the diastolic pressure used for the prediction only was measured after four days of shock and would not have been useful for guiding therapy.

Based on retrospective data in patients with cardiogenic shock, Rigamonti et al. stated that diastolic pressure was the only predictor of outcome. This study is important for this debate because it demonstrates an example of flaws in reasoning in this area [9]. The differences in diastolic pressure between survivors and non-survivors only were 4 mmHg and both were low; 37 ± 8 mmHg in non-survivors and 41 ± 7 mmHg in survivors. In contrast, a larger study showed that systolic pressure while on vasopressors is a strong indicator of the risk of death and diastolic pressure did not enter into their logistic model [10]. Why the difference? Patients only were included in the Rigamonti study [11] if the blood pressure was <90 mmHg, which means that patients with higher systolic pressures and low diastolic pressures were

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excluded; this created a selection bias in favor of the "independent" value of a low diastolic pressure. Survivors and non-survivors had the same minimum and maximum cardiac index and almost half of those who died had a normal cardiac index. Thus, it is likely that about half the patients had a component of distributive shock and not pump failure, which is what would be expected if inadequate coronary perfusion was the primary problem. About a third of patients in the Rigamonti study had an intra-aortic balloon pump inserted (IABP) [9]. The IABP is used to decrease left ventricular afterload by decreasing diastolic pressure before left ventricular ejection and by increasing mean diastolic pressure by inflating the balloon. In the patients with an IABP, "lowest" diastolic pressure was lowered by the IABP, but their mean diastolic pressure was likely higher than normal because the balloon inflation augments diastolic pressure. This association with the IABP could have confounded the predictive value of diastolic pressure for presumably the IABP patients were sicker but we do not know the distribution of IABP use in survivors and non-survivors. Lowering diastolic and systolic pressures with the IABP could have led to an unnecessary increase in norepinephrine if mean pressure was used to guide vasopressors. Of note, despite the significantly lower diastolic pressure, the presumably more important marker of cardiac risk, coronary perfusion pressure, was the same in survivors and non-survivors in this study [9]. In the large percentage of patients with distributive shock in this and other studies of patients with cardiogenic shock [10] [12-14], treatment needs to be aimed at the cause of the distributive component, which is likely related to cytokine activation from bacterial leak from the gut, an ongoing infection, or tissue injury because of poor matching of blood flow to tissue needs [12-16].

A number of issues in clinical reasoning need to be considered in these studies. First, the data only is associative and not causal; there is no evidence that increasing diastolic pressure alters outcome. A statistical fallacy also could have contributed to the predictive value of diastolic pressure [9]. When comparing two populations two key variables are the number of subjects and the variance of the values in each group. The range of diastolic values usually is narrower than systolic values. Thus, because variance is lower but the subject numbers are the same, the threshold for statistical significance is lower for diastolic than systolic pressure as observed in the Rigamonti study [12].

There also is a potential clinical confounder. Mean arterial pressure is regarded as the best value to use for vasopressor management [17] and it was the clinical target in all the quoted studies. However, in distributive shock, the low diastolic pressure lowers mean pressure, even when the systolic pressure is adequate for tissue needs and even coronary flow. This lower mean pressure then drives up use of catecholamine which is associated with increased tissue injury [18-20]. In the Katz study, systolic pressure was one of the best indicators of a favourable outcome [10]. Perhaps use of systolic pressure with a combination of invasive and non-invasive techniques, including auscultation and palpation, to improve the accuracy of the measurement, might be better than use of mean pressure.

What can the physiology tell us? Arterial pressure is determined by cardiac output, systemic vascular resistance and critical closing pressures at the level of the arterioles [21]. Raising blood pressure with just an increase in systemic vascular resistance does not improve oxygen delivery to tissues unless some regions gain while others loose [21]. If there is no change in blood flow distribution, blood pressure increases but regional flows, including the heart, do not. When high concentrations of vasopressors are used, it is likely that no region benefits if cardiac output does not increase. Thus, treatment of shock requires an increase in flow and pressure and treatment needs to be personalized [22]. Direct measures of cardiac output are ideal but markers of better tissue perfusion such as reduction of lactate, increased urine output, improved sensorium, and increased central venous saturation can be helpful.

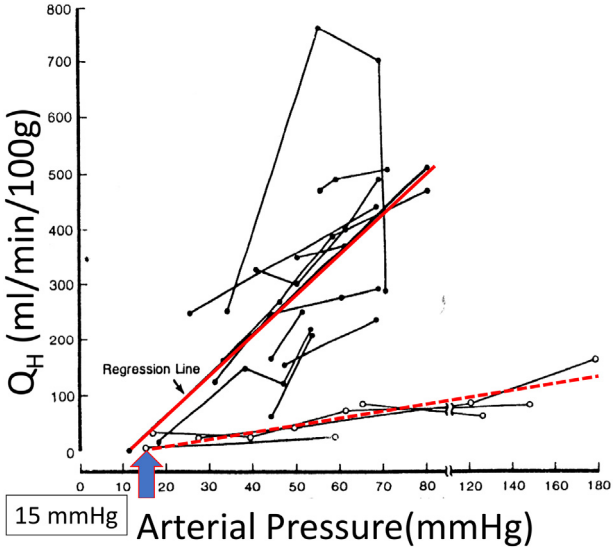

Fig. 1. Plot of blood flow to the heart (Q_H) against mean arterial pressure. Blood pressure (mean) was progressively lowered in dogs by step-wise hemorrhage and blood flow measured with radio-labelled microspheres (4 points per animal). Open circles represent animals with no vasodilators; closed circles represent animals maximally dilated with nitroprusside. The hearts were still functioning with a mean arterial pressure of 15 mmHg and coronary reserves were not yet reached (up arrow). Adapted from ref. [23].

Regional flows, including myocardial blood flow, are determined by the generated arterial blood pressure and regional vascular resistances. Accordinlgy, the ratio of diastolic pressure to coronary vascular resistance determines coronary flow to the left ventricle. Coronary flow reserves are large; it can increase from 80 ml/min/100 g of tissue at baseline cardiac output to almost 500 ml/min/100 g at peak performance. In dogs with normal coronary arteries, coronary reserves were not exhausted even at a mean pressure of <20 mmHg (Fig. 1) [23]. Furthermore, myocardial oxygen need decreases with decreasing systolic pressure, and thereby reduces the need for coronary blood flow. Finally, an unappreciated point is that the compliance of the large epicardial coronary conductance vessels accumulate volume during systole. This stored volume then contributes to coronary flow during diastole [24-26]. Thus, systolic pressure still contributes to left heart blood flow.

The sub-endocardial surface of the heart is more vulnerable to ischemia than the epicardial layers. In both animal and human studies [4,27], this vulnerability is related to the ratio of the area under the left ventricular systolic pressure-time curve relative to the area under the diastolic pressure-time curve but not the actual diastolic pressure which further argues against isolated use of diastolic pressure.

In conclusion, a low diastolic pressure is a marker of poor outcome, but it should not be used as a target to guide therapy. To do so can lead to overuse of vasoconstricting drugs which increase vascular resistance without changing tissue perfusion. Management of shock needs to combine flow measurements with pressure measurements and should include assessment of clinical markers of adequate perfusion. Diastolic pressure is determined by the volume in the aorta. When diastolic pressure is low and cardiac output is normal or elevated, the question should be where did the volume go, to which tissues, and why?

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Importance of diastolic arterial pressure in septic shock: Rebuttal to comments of Dr. Magder

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We read with great interest the paper by Dr. Magder, who is undoubtedly one of the most brilliant scientists working in the field of intensive care. Nevertheless, the majority of the arguments developed against the importance of the diastolic arterial pressure (DAP) in his paper referred to 1) patients with cardiogenic shock, in general or treated with intra-aortic balloon pump, 2) to patients in the post-partum with severe hemorrhage, and 4) to normal dogs with normal coronary arteries submitted to experimental hemorrhage (as illustrated in the figure of his paper). Yet, according to its title, this pro-con debate should focus on patients with septic shock. Such patients have a high risk to die, especially when resuscitation is late and/or inappropriate. At the early phase, only the clinical context including clinical examination, is available and not taking into account all the available information to make appropriate therapeutic decisions can be catastrophic for the patient's outcome. Arterial blood pressure is a very important parameter not only because it is physiologically regulated (unlike cardiac output) but also because it contains a lot of useful information that clinicians cannot ignore. The DAP is one of this. Observing a low DAP in patients with shock, especially in cases of tachycardia, strongly indicates that a low vascular tone is a significant component of the shock state. This can help to quickly make the diagnosis of the vasodilatory nature of the shock state (most often septic shock) and to consider the potential use of vasopressors. Surprisingly, Dr. Magder has not elaborated on this important point. Furthermore, he has minimized the major role of the DAP as the upstream pressure for the perfusion of the left ventricle and rather has highlighted the importance of the systolic arterial pressure, which is physiologically far less involved in the coronary blood flow of that ventricle. The importance of the DAP has been indirectly highlighted by large cohort studies in patients with coronary artery disease treated for arterial hypertension (more than 22,000 patients…!), that showed that the DAP but not the systolic arterial pressure was associated with outcome [1]. A DAP lower than 70 mmHg was significantly associated with mortality [1]. Therefore, 1) as a great proportion of patients with septic shock have cardiovascular comorbidities including known or unknown coronary artery disease, and 2) as more than 50% patients with septic shock have reduced coronary flow blood reserve [2], it is hard to consider that DAP is of little interest in the management of patients with septic shock.

Conflict of interest

JLT is a member of the Medical advisory board of Pulsion/Getinge. OH has no conflict of interest to declare.

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Importance of diastolic pressure in septic shock: Con – Response

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Response to JL

In response to my good friends, Dr.'s Hamzaoui and Teboul, I will start by saying that we agree on some things. The data is poor; it only is associative, and none is randomized. This likely explains why the Surviving Sepsis program dropped treatment of a low diastolic pressure. We also can agree that treatment of a low diastolic, and I would add systolic pressure, is likely important in patients with significant coronary artery disease or those with severe pulmonary hypertension. Because of the lack of data, we argued physiology, but we also should agree that physiology predicts nothing but explains everything after the fact!

My friends argue two basic points. Diastolic pressure is an indicator of decreased vascular tone and, secondly, diastolic pressure is a determinant of coronary perfusion. They should also note that diastolic pressure is an approximate indicator of left ventricular afterload. Raising diastolic pressure increases myocardial oxygen demand and shifts the cardiac function curve downward.

I agree that a low diastolic pressure indicates decreased vascular tone, but it also means that coronary vascular resistance is decreased, and thus a lower perfusion pressure is needed to perfuse the heart. The need for coronary flow, too, should be lower because myocardial oxygen demand is lower.

The study by Dhainaut et al. [1] referenced by my colleagues truly is a landmark paper and provides much physiological data for our mutual speculations. Almost all the septic patients had higher coronary blood flows than non-septic subjects. Even the 6 subjects with *mean* arterial pressures less than 50 mmHg had coronary flows equal to, or greater than the normal subjects. Two of these 6 died (33%), but this is the same percentage of deaths as in those with higher mean arterial pressures. The fact that the study could even have been done in these patients makes my point! Non-survivors had greater coronary blood flow than non-survivors and less oxygen extraction. Even mean cardiac output was higher. This, plus the change in metabolic profile the authors elegantly documented, points to a tissue metabolic problem rather than inadequate flow as the primary problem. Furthermore, the authors specifically made the point that there were no ischemic ECG changes. This reflects my experience. I would ask my good friends how often have they seen acute ST elevations in the hundreds to thousands of septic patients they have treated over years?

The assessment of coronary reserve in septic patients by Ikonomidis et al. [2] also is of interest. Patients who died had a lower average coronary flow reserves than survivors, but reserve values were less than reported normal values in both groups. This again likely reflects a greater metabolic-perfusion mismatch in those who died. Surprisingly, even though the Apache was only17.5, lactate1.9 mmol/L, and mean arterial pressure greater than 78 mmHg, more than 50% died. Catecholamine usage was not reported but it is possible that excessive catecholamine use blocked normal flow reserves and contributed to deaths.

A low blood pressure value is meaningless without knowledge of cardiac output. What if diastolic pressure is low and CI is 2.2 L/min/m^2 in one patient and 4.0 L/min/m^2 in another? Should they be treated the same? How inadequate can coronary blood flow be if the heart is working well? The heart has minimal anaerobic reserves and inadequate coronary flow should result in an immediate decrease in cardiac function and a further decrease in arterial pressure. In the patient with the high cardiac output I would consider decreasing norepinephrine if the dose were high. Increasing arterial pressure by vasoconstriction, and without an increase in cardiac output cannot increase coronary flow unless some other region loses blood flow. It also increases myocardial oxygen demand.

Coronary arteries have an advantage for obtaining flow in diastole over other tissues. Myocardial contractions empty blood from intramyocardial vessels as occurs during contraction of skeletal muscles. Thus, coronary arteries start diastole with lower pressures than other tissues and should preferentially obtain more of the available diastolic flow. The build up of epicardial volume in systole also produces a reserve for immediate initial diastolic coronary flow [3].

My colleagues quote the association of low arterial pressures with increased events in studies of antihypertensive patients. However, despite the associations, the most recent American Heart Guidelines [4] maintained the current tight control for all, but advised clinicians to moderate targets in patients who are symptomatic with low blood pressures [5]. Use of an antihypertensive is clearly different from use of a vasopressor but the same clinical wisdom likely applies. If there is no evidence of ischemia, I would not treat a diastolic pressure and an elevated troponin is not a symptom!

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