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Inodilator versus inotrope: do inodilators have an edge to improve outcome in patients with heart failure or cardiac dysfunction?

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ABSTRACT

Numerous meta-analyses on inotropes (dobutamine) and inodilators (milrinone, levosimendan) suggest that their impact on survival are at best neutral (but may be deleterious) whereas levosimendan seems to have beneficial effects on survival in patients with acute heart failure (AHF) syndromes. The aim of this essay is to attempt to explain these results through a conceptual framework of cardiocirculatory (patho)physiology. Many clinical studies in AHF have been based and interpreted on a 'cardiocentric' framework. The three above-mentioned categories of drugs are thought to increase cardiac output (CO) by increasing only heart muscle contraction (inotropes) or by also decreasing systemic vascular resistance (inodilators). We complement this 'cardiocentric' framework with a more integrated one based on (i) the effects of drugs on venous return (VR), equal to CO (VR is the difference between mean systemic and right atrial pressures divided by venous resistance; maintenance of adequate VR depends on the stressed blood volume); inodilators may decrease the stressed volume and therefore may decrease VR; (ii) the coupling of the left ventricle–aorta and right ventricle–pulmonary artery (dependent on the compliance of the large arteries), which is increased by inodilators in the absence of measurable effects on arterial systemic/pulmonary pressures) and (iii) the vascular waterfall phenomenon, which explains that inodilators, by decreasing intra-organ arterial resistance, can improve organ perfusion even in previously mildly hypotensive patients (in the absence of cardiogenic shock). The challenge is to transform these concepts into clinical tools to guide therapy in AHF syndromes.

Key words: haemodynamics, contractility, vasodilation, inotropes, inodilators, levosimendan

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Introduction

The use of beta-blockers in chronic heart failure was, in effect, prohibited 25 years ago because the interpretation of physiology was considered to make their use reckless and dangerous. In the years since, re-appraisal of the interplay between physiology and pharmacology has created a situation in which the use of beta-blockers in chronic heart failure is almost mandatory, and the *withholding* of these drugs is now considered reckless and dangerous.

As the fortunes of beta-blockers have risen so the status of inotropic drugs has faded. In recent years, however, there has been a new interest in these drugs

and, in particular, an interest, also grounded in re-appraisals of physiology, in differentiating between drugs that are exclusively inotropic and drugs that also act to dilate parts of the vascular system, arterial or venous.

Knowledge, clinical practice and clinical studies on this question are based on the following concepts and premises (Fig. 1).

- (i) A pure inotrope would increase heart muscle contraction, although this is difficult to measure directly in clinical practice (e.g. dP/dt measurements for ventricular contractility) and is often assessed using a surrogate such as cardiac output (CO) or, less frequently, left ventricular (LV) ejection fraction (LVEF).

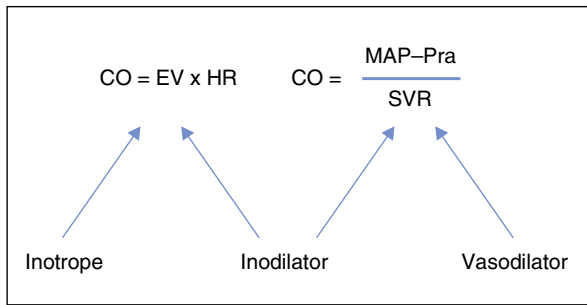


Figure 1. The ‘cardiocentric’ view of the mechanisms of an inotrope, an inodilator and a vasodilator. A pure inotrope would theoretically increase ejection (stroke) volume. An inodilator would increase ejection volume and decrease systemic vascular resistance. A vasodilator would decrease systemic vascular resistance. CO — cardiac output; EV — ejection volume; HR — heart rate; MAP — mean arterial pressure; Pra — right atrial pressure; SVR — systemic vascular resistance

- (ii) An inodilator would do (i) and would also decrease systemic vascular resistance to some extent (the precise balance of effects would vary from drug to drug).

Within this conceptual framework, many individual studies have been performed; more recently, a series of meta-analyses have been undertaken, the results of which may be summarized as follows.

- Dobutamine is at best neutral in terms of outcome (survival) compared with placebo in patients with end-stage cardiac failure [1]. Several studies found dobutamine to be associated with a worse outcome than placebo in patients with myocardial dysfunction after cardiac surgery [2]. However, these data did not establish a cause-effect relationship for this finding.
- Milrinone, an inodilator that works primarily through inhibition of phosphodiesterase (PDE)-III, with only a 14-fold selectivity for PDE-IV [3], is at best neutral *vis-à-vis* placebo in terms of outcome in patients with heart failure and appears to have deleterious effects when only more methodologically robust studies are considered [4].
- Levosimendan, a calcium-sensitizing agent, is associated with improved outcome in several clinical settings such as after cardiac surgery [5, 6] or surgical coronary revascularization [7], in ICU patients [8], and in patients with acute decompensated cardiac failure treated outside the operating theatre or ICU [9]. A meta-analysis published in 2010 concerning patients with acute heart failure suggested that levosimendan improved survival when compared with dobutamine but not versus placebo [10].

Meta-analyses may be criticized [11], but it is reasonable to assume that similar methodological limitations apply to all meta-analyses of inotropes and inodilators. Furthermore, while meta-analyses tell us which drugs affect/do not affect outcomes they do not reveal why or how individual drugs exert their effects. For answers to these questions, we must refer to physiology and pathophysiology, two fields of medicine that are frequently overlooked in day-to-day practice. The goal of this essay is to attempt an explanation of how and why inodilators (and by extension inotropes) do/do not improve outcome.

The first explanation, on which probably most investigators and clinicians would agree, is that despite efforts to better define the phenotypes of acute, chronic or chronic decompensated ‘heart failure’ the problem is still complex and that in both prospective randomized trials and meta-analyses there is impressive heterogeneity among patients diagnosed with heart failure. Noticeably, improved haemodynamic status, estimated by a variety of endpoints, is not always associated with improved survival in either the short or long term [12].

The second explanation, perhaps less obvious, is that our view of the cardiocirculatory system, in both normal and pathophysiological circumstances, is ‘cardiocentric’. This is substantially due to the availability of monitoring devices (e.g. the pulmonary artery catheter and echocardiography) that provide easy access to predominantly cardiac indices. In the next part of this essay, we will attempt to complement this ‘cardiocentric’ view with an integrated view of the cardiocirculatory system.

Cardiocentric versus an integrated view of the cardiocirculatory system

In the ‘cardiocentric’ view, CO is the product of LV ejection (stroke) volume and heart rate. In the integrated view, at equilibrium (i.e. within the time frame of several heartbeats), CO and venous return (VR) are equal. VR is determined by blood volume, venous tone and cardiac activity [13–15]. Of note, the right and left venous returns must be nearly equal.

Blood volume is mainly located within the venous system (60–70% of total blood volume), with the remainder distributed among the heart, lungs, arteries and arterioles [13, 14]. The total blood volume (V_t) is the sum of:

- (i) the *unstressed* blood volume (V_u ; the volume necessary to fill the circulatory system to its maximum capacity without an increase in the transmural pressure), and
- (ii) the *stressed* blood volume (V_s ; the difference between V_t and V_u).

Vu is haemodynamically 'inactive' because for a given global performance of the cardiocirculatory system it is not altered by its changes in capacity (for an unchanged value of the venous compliance). Vu can decrease either by venoconstriction (initiated, e.g., through activation of the sympathetic nervous system [SNS] or the actions of drugs such as alpha₁-adrenergic agonists) — which results in part-conversion into Vs — or increase by venodilation in response to drugs that relax the vascular smooth muscle cells (including vasodilators and inodilators); this increase in Vu would be associated with a decrease in Vs.

Vs accounts, in normal physiological circumstances, for ~30% of Vt and is haemodynamically active [16] (contributes to global cardiocirculatory performance through increased VR).

Vs/Vu ratio can change even in the absence of a change in Vt and thus modify the percentage of blood volume that is haemodynamically active [16]. Mobilization of the blood volume by activation of the SNS can involve up to 30% of Vt with two-thirds of this 30% coming from the splanchnic venous circulation [16]. Of note, pharmacologically induced constriction of venous smooth muscle cells can result in decreased compliance and increased Vs, but also in increased venous resistance (Vres), notably of the hepatic veins [16]. The global result could thus be a decreased VR despite an increase in Vs. Vasodilators and inodilators, which are the focus of this article, would decrease Vs and would have the capacity to decrease VR (Fig. 2).

The determinants VR [13, 14] are mean systemic pressure (Pms), right atrial pressure (Pra) and Vres, as shown in **Equation 1**:

$$VR = Pms - Pra / Vres = CO$$

The determinants of Vres are blood viscosity (h), the length of the venous system and the radius of the veins, and are shown in **Equation 2**:

$$Vres = 8hl / pr^4$$

where h is mainly dependent on haematocrit (h decreases with a decrease in haematocrit) and blood temperature (h increases with hypothermia) and can be changed acutely by a decrease in haematocrit through haemodilution secondary to volume expansion with sanguinous volume expanders.

Pms is derived according to **Equation 3**:

$$Pms = Vs / C_{sv}$$

where C_{sv} is the mean compliance of the venous system that contains Vs. As mentioned previously, Vs is the difference between Vt and the Vu, as shown in **Equation 4**:

$$Pms = (Vt - Vu) / C_{sv}$$

Equations 3 and 4 show that Pms can change as a result of changes in:

- Vt
- Vs/Vu ratio
- C_{sv}

If a vasodilator increases C_{sv}, Pms will decrease and, all other variables being equal, so will the VR. Hence CO will either decrease or will be maintained by an increase in HR through activation of the baroreflex even if the drug in question is not directly a positive chronotropic drug [16]. This may be the case for inodilators if the decreases in Pms and VR are not recognized and are not corrected by volume expansion.

One of the reasons the physiology of VR has not gained the attention of the medical community in routine clinical practice is because measurement of Pms requires an arrest of cardiac activity. This can be performed fairly easily in experimental animals and exceptional clinical situations (e.g. when inducing heart fibrillation to test an implantable defibrillator), but its measurement in routine clinical practice has been difficult. Recently, Maas and colleagues have proposed three methods of measuring or calculating Pms [17–20].

The first method consists of stepwise increases in intrathoracic pressure in mechanically ventilated and sedated patients that allows the determination of Pms through extrapolation. The second method consists in rapidly (< 1 sec) inflating a cuff around the arm at a pressure 50 mmHg above the patient's systolic blood pressure. In this situation, the rapid inflation attenuates/eliminates venous stasis and the pressure that is measured (in the radial artery catheter) is equal to that in the arm circulation (arterial and venous) distal to the inflated cuff. The third method exploits a calculation for which the only directly derived data required are the Pra and CO.

The authors of these methods showed that all three techniques provide results for Pms but that the calculated Pms systematically overestimates the measured value [17–19]. It must be admitted that, with the exception of the technique of rapid cuff inflation, these investigations do not lend themselves to use in routine clinical practice (even the cuff method requires a dedicated device).

The authors compared their results for **Equation 1** with results obtained in animals and found that, in both settings, the difference between Pms and Pra is only ~10 mmHg. This is a fairly low-pressure gradient, well within the margins of error when measuring venous pressures in clinical practice. This implies that any estimation of VR will be prone to error. This probably explains, at least to some extent, why clinical reasoning is predominantly cardiocentric. Figures 1 and 2 outline the 'cardiocentric' and integrated paradigms for the actions of vasodilators, pure inotropes and inodilators.

A brief overview of venous physiology

The global venous system contains approximately 70% of Vt but this percentage can vary according to

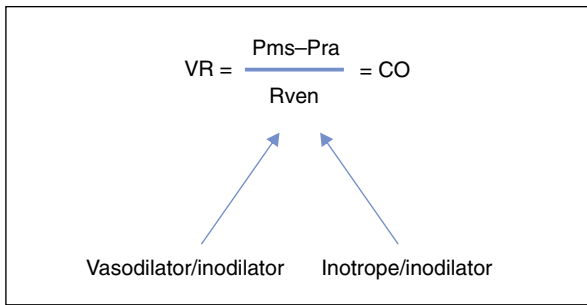


Figure 2. Integrated view of the mechanisms of an inotrope, an inodilator and a vasodilator. A vasodilator or an inodilator would decrease mean systemic pressure and could, therefore, be able to decrease venous return and therefore cardiac output (in the absence of a reflex increase in heart rate). VR — venous return; Pms — mean systemic pressure; Pra — right atrial pressure; Rven — venous resistance; CO — cardiac output

a particular organ. Within the venous compartment, small veins and venules contain 70% of Vt. Pressure values are 10–15 mmHg in small veins and venules, 4–8 mmHg in the peripheral hand veins and 1–2 mmHg in the vena cava. Portal venous pressure is 7–10 mmHg [16, 21].

One venous circulation of particular importance in physiology and pathophysiology is the splanchnic venous circulation, which contains ~25% of Vt [16, 21]. Because of the very dense sympathetic innervation of the splanchnic veins, this ‘splanchnic reservoir’ can be mobilized through decreased compliance and a reduction in vein diameters. This sympathetic-mediated mobilization is, in fact, the reason why blood loss equalling 10–15% of the blood volume is not associated with decreased blood pressure or CO. Globally, the venous circulations of different organs are less prone to regulation by local metabolites and more susceptible to modulation by the SNS.

Csv is the ratio of a change in volume (DV) to the concomitant change in transmural distending pressure (DP) = DV/DP. It is a quantitative measure of the elasticity of a vascular bed. Systemic venous compliance is at least 30-times higher than arterial compliance [16, 21]. The compliance of the systemic circulation is 7-times higher than that of the pulmonary circulation and this is extremely important for right ventricle–pulmonary artery coupling (see below). After a change in CO, changes in compliance are observed mostly in the systemic circulation and, to a much smaller extent, in the pulmonary circulation. However, the compliance of pulmonary veins can be increased following the administration of a venodilator drug such as nitroglycerin or a prostacyclin analogue and, probably, sildenafil [22]. Of interest, the compliance of the pulmonary veins is decreased in LV failure, whether with altered or preserved LVEF. Much less is known about the compliance of the pulmonary

artery, but recent data from our laboratory suggest that pulmonary arterial and venous tone are similar, at least as far as the *in vitro* response to noradrenaline is concerned [23]. The decreased compliance of the pulmonary artery, as can be observed in congestive states, could render it less elastic and thus alter right ventricle–pulmonary artery coupling (see below). Compliance in the venous, systemic and pulmonary circulations can, of course, be changed by vasodilators and inodilators.

It must be emphasized that there are situations in which changes in Vu and compliance are concordant (e.g. venoconstrictors would decrease both parameters, whereas venodilators would increase them), but there are also situations in which the changes in Vu and compliance are discordant [16].

To add to the complexity, venoconstrictors can increase Vres whereas venodilators decrease it. Although Vres is much smaller than arterial resistance, changes in Vres must be interpreted in the context of the small pressure gradient in the venous circulation (**Equation 1**). Increased Vres, particularly in the hepatic veins, can result in blood stagnation in the splanchnic venous circulation, an increase in portal vein pressure, an increase in capillary filtration and inefficient mobilization of Vs [16]. One of the most powerful humoral mediators in this context is angiotensin II, which results in increased portal vein pressure secondary to increased hepatic vein resistance [16]. The determinants of Vres are shown in **Equation 2**. It is to be noted that an acute change in h (as observed with acute haemodilution in the presence of normovolaemia) would result in decreased Vres and thus increased VR. By contrast, haemodilution in the presence of hypovolaemia would probably not increase VR because of the increase in hepatic vein resistance effected by the SNS.

It is also important to remember that anaesthesia may profoundly modulate the effects of venoconstrictors [16] and venodilators compared with the non-anaesthetized state. Among other mechanisms, anaesthesia alters the buffer effects of the baroreflex. Whether sedation (a ‘lighter’ form of anaesthesia) produces effects intermediate between the awake and the anaesthetized states is unknown.

Ventricle–large artery coupling

The arterial system, both systemic and pulmonary, acts as a conduit to deliver blood to the systemic and pulmonary circulations. It also acts as a ‘shock-absorber’ to soften the pulsations generated by the heart such that capillary blood flow is almost continuous [24]. Central vessels (i.e. the proximal aorta and pulmonary artery) exert their cushioning function by virtue of their

Table 1. A brief overview of the arterial elastance/ventricular elastance (E_a/E_{es}) ratio in health and disease

- In normal individuals, the E_a/E_{es} ratio is 0.7–1.3
- There is a physiological increase in aortic E_a with age, due to stiffening of large arteries
- There is a physiological increase in E_{es} with age – the E_a/E_{es} ratio in healthy elderly patients is maintained close to 1
- In patients with congestive heart failure, the E_a/E_{es} ratio can be up to 4 due to:
 - decreased E_{es} (decreased systolic function)
 - increased E_a (via multiple mechanisms)

high content of elastin; distal systemic arteries contain progressively less elastin and more collagen. With ageing, the aorta stiffens (albeit much less is known about the effects of ageing on the proximal pulmonary artery). This stiffening of the aorta is manifested clinically in the increased pulse pressure observed in elderly patients [24], and explains why even a normal stroke volume results in higher systolic pressure; it also explains why a higher percentage of the stroke volume is forced into the peripheral arterial tree in older persons. This probably also results in a lower volume of blood in the proximal arterial tree during diastole and could be one explanation for the lower diastolic pressure observed in the presence of stiffening aortas [25].

The stiffening of the aorta is responsible for an increase in pulse wave velocity (from 5 m/sec in young adults to 10 m/sec in elderly patients). The antegrade wave is reflected in the periphery (at the level of the renal arteries for the lower body). The reflected wave will travel more rapidly in stiff aortas, and instead of reaching the proximal aorta in late systole or early diastole, as in normally elastic aortas, it will arrive in early systole thus increasing the systolic pressure and the left ventricular work. The loss of the reflected wave in diastole explains the reduction in diastolic pressure, which is the driving pressure of the coronary circulation.

Under physiological conditions, the functions of the ventricles (left or right) and their associated major arteries are coupled. From a pressure–volume curve (Fig. 3) it is possible to calculate the ventricular end-systolic pressure–volume relationship. By changing the preload through vena caval occlusion (in experimental animals) or by the injection of a pure alpha-adrenergic agonist in humans [26] it is possible to generate a family of ventricular pressure–volume curves, the end-systolic points of which are aligned on a straight line. This line represents the LV elastance (E_{es}) and its slope is an estimate of ventricular inotropism — the more vertical the slope, the higher the inotropic function. The ventricular afterload may be quantified as the effective arterial elastance (E_a), which is the ratio between ventricular end-systolic pressure and the stroke volume.

The ratio of E_a/E_{es} is close to 1 (ventriculo-arterial coupling) under physiological conditions. Table 1 illus-

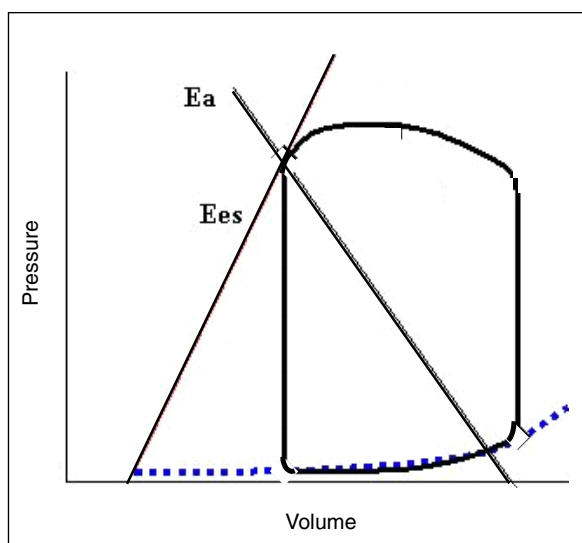


Figure 3. Ventricular and large artery elastances. E_a — arterial elastance; E_{es} — ventricular elastance

trates some of the changes that may be encountered under both physiological conditions (i.e. ageing) and during cardiac failure.

Alteration of ventricular–large artery coupling will put the ventricle into a deleterious energetic situation. The most impressive illustration of the impact of increased E_a (stiffening of the aorta) comes, paradoxically, from humans with aortic valve stenosis. Many clinicians believe that the increased afterload of the left ventricle in patients with aortic stenosis comes from the decreased surface of the aortic valve. Accordingly, few would dare use a vasodilator such as sodium nitroprusside because of the fear of decreasing preload. However, Khot et al. [27] demonstrated that in patients with severe aortic stenosis and low LVEF, who were in critical circumstances while awaiting aortic valve surgery (pulmonary oedema and severe dyspnoea), sodium nitroprusside increased cardiac index, with a minimal decrease in the aortic pressure and no increase in heart rate. The most plausible explanation, based also on simulations from clinical data [28], is that sodium nitroprusside was able to improve left ventricle–aorta coupling. This

example illustrates the importance of considering left ventricle–aorta coupling, and not only the effects on SVR when analysing the effects of vasodilators.

There are several lines of evidence indicating that inodilators (e.g. levosimendan) can restore the Ea/Ees ratio to normal, with minimal changes in mean arterial pressure (Pa). This has been nicely demonstrated by Guarracino et al. [26] in patients who underwent coronary artery bypass graft surgery. These authors demonstrated that in patients who did not have severe alteration of LV function but already had an abnormally high Ea/Ees ratio, levosimendan was able to restore the Ea/Ees ratio to a normal value. Of interest, because these patients did not have heart failure or were not in a congestive state, levosimendan also decreased preload (and hence ejection volume) and activated the baroreflex, so increasing the heart rate. This is also probably what happened in the SURVIVE study [29].

The impact of an altered Ea/Ees ratio on the left ventricle has been appreciated for many years, but only in a more recent study has it been demonstrated that similar effects operate meaningfully in the pulmonary circulation [30]. In normal dogs, Ees was 1.17 and Ea was 0.64, with a resulting Ees/Ea ratio of 1.81. In dogs with experimental heart failure, borderline pulmonary arterial hypertension and right ventricular dysfunction, Ees was 1.46 and Ea was 1.90 (due to the high pulmonary Pa values), with an Ees/Ea ratio of 0.7. Milrinone was able to bring the Ees/Ea ratio back towards normal values (Ees increased to 2.43 with an unaltered Ea of 1.9, resulting in an Ees/Ea ratio of 1.28). Several other reports, mainly involving paediatric patients, suggest that an alteration of the pulmonary artery pulsatility (just as for the systemic circulation) is associated with worse outcomes [31]. Experimental models also demonstrate that decreased compliance of the pulmonary artery, mainly due to loss of elastin, alters right ventricle–pulmonary artery coupling [32]. We hypothesize that in addition to structural changes in the pulmonary artery, altered right ventricle–pulmonary artery coupling might be secondary to decreased pulmonary artery compliance because of acute pulmonary artery dilatation secondary to both congestions and to altered pulmonary artery–vein coupling. The increased stiffening of the pulmonary veins is probably secondary to altered LV function (both systolic and diastolic) and decreased compliance through activation of the SNS.

Drugs, such as vasodilators and inodilators (including levosimendan), that increase pulmonary vessel compliance could improve right ventricular function [33, 34]. Given the fact that the compliance of the pulmonary circulation is 7-times less than that of the systemic circulation, it is easy to imagine that alteration of the compliance of the pulmonary circulation will be

an initial event in cases of congestion. Alteration of the ventricular–large artery coupling, both left and right, is not easily measurable in clinical practice and is not visible from the measurement of CO, Pa or calculation of the systemic or pulmonary vascular resistance. In a recent population study of patients with heart failure (both with altered and preserved LVEF), pulmonary hypertension (defined as pulmonary artery systolic pressure > 35 mmHg) was found in 79% of the 1046 patients [35]. Pulmonary arterial hypertension was not associated with LV systolic dysfunction but was associated with diastolic dysfunction. The mechanisms incriminated were the passive backward transmission of the elevated LV end-diastolic pressure to the pulmonary veins associated with active vasoconstriction and remodelling of the pulmonary arteries (intimal fibrosis, medial hypertrophy). All above-cited mechanisms will decrease the compliance of the pulmonary circulation and alter the right ventricle–pulmonary artery coupling.

The vascular waterfall phenomenon

Total SVR is calculated as $SVR = (Pa - Pra)/CO$, based on the concepts taken from the electrical circuit theory. Such calculation of the SVR implies a constant pressure decrease from the input to the output pressure.

If this concept were true, when the flow is zero, then Pa should equal central venous pressure (Pcv). In fact, numerous experimental settings have demonstrated that this concept of constant pressure decrease is false. It was demonstrated in the canine coronary circulation that when the coronary flow was zero, the pressure was 30–50 mmHg while Pcv was 5–10 mmHg (see Magder [36] and references therein). These results are explained by the fact that there are two in-series resistors. The first is arterial, from the input Pa to the arterial critical closing pressure (Pcc; defined as the pressure under which the flow from the arterial to the venous side of the circulation is stopped despite the persistence of a pressure gradient). The second resistor is venous, from the Pms to the Pra (see **Equation 1**). The pressure decrease between Pcc and Pms is called the vascular waterfall or Starling resistor [36]. The Pcc can be measured in experimental settings [36] or calculated in patients [37]. These concepts are illustrated in Figure 4. Total vascular resistance (SVR for the systemic circulation) does not exist from a physiological point of view and the calculated SVR exceeds the sum of the arterial (Ra in Figure 4) and venous (Rves) resistances. Experimentally, but also in clinical practice, it has been shown that Pcc is the site of action of vasoactive drugs (vasodilators and vasoconstrictors) [38] and is also regulated by the SNS [37]. Vasoactive drugs and interventions such as

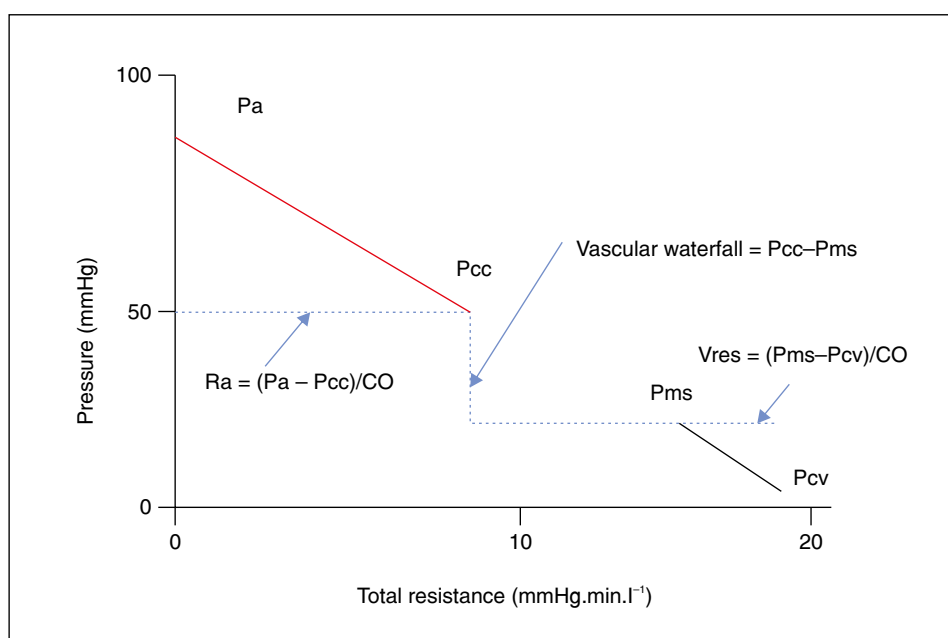


Figure 4. Representation of the total systemic vascular resistance as the sum of the arterial resistance (R_a) and the venous resistance (R_{ven}). P_a — input arterial pressure; P_{cc} — critical closing pressure; P_{ms} — mean systemic pressure; CO — cardiac output; P_{cv} — central venous pressure. Modified from Maas et al. [37]

volume expansion could act differently on the arterial and venous resistors, and flow through vital organs is regulated in a more complex manner than can be accounted for by calculation of the SVR. The physiological significance of the vascular waterfall has been summarized by Magder [36] as follows.

- (i) Flow to organs that autoregulate (heart, brain, kidney) is regulated not by the P_a - P_v gradient but by the P_a - P_{cc} gradient. If a vasodilator or inodilator decreases both P_a and P_{cc} similarly or P_{cc} more than P_a , the intra-organ flow will be maintained or even increased. Interestingly, maximum vasodilation will not eliminate the vascular waterfall [39]. The vascular waterfall phenomenon could explain the results of Mebazaa et al. [40] which showed that in patients with heart failure, vasodilators, but also levosimendan, improved survival even in patients with systolic hypotension. On the contrary, if an inotrope/vasoconstrictor increases the P_{cc} more than the P_a , the intra-organ resistance will increase and the flow will decrease.
- (ii) The existence of the Starling resistor at the level of arterioles explains why an increase in P_v (Valsalva manoeuvre or cough), though it increases V_{res} , will not decrease the P_a - P_{cc} gradient and flow within the organ will be maintained.
- (iii) The presence of the Starling resistor explains why, in case of a sudden decrease in CO , the pressure will not drop as rapidly, and the flow to vital organs such as the brain and the heart will be to some extent preserved.

The P_{cc} values are lower in the brain and the heart than in other territories [37], such as the lower limb.

From this brief overview of physiology, it seems obvious that clinically familiar haemodynamic concepts cannot fully explain the complexity of effects that occur when a vasoactive drug is administered to a patient. The deleterious effects of pure inotropes in patients with heart failure or myocardial dysfunction after cardiac surgery or in the ICU are probably due to the fact that these drugs may:

- (i) increase heart rate more than the ejection volume, with a resultant increase in myocardial oxygen consumption
- (ii) not be efficient in patients under chronic beta-blocker therapy
- (iii) result in rapid desensitization and downregulation of the β_1 -adrenergic receptors
- (iv) decrease P_{ms} through β_2 -adrenergic agonist effects and therefore decrease VR
- (v) not improve ventricular-large artery coupling by not improving large artery compliance
- (vi) increase the intra-organ arterial resistance by increasing P_{cc} .

By contrast, inodilators could have potential beneficial effects in this situation by virtue of:

- (i) having less positive direct chronotropic effects, though activation of the baroreflex could still result in increased heart rate
- (ii) being effective in patients receiving chronic [41] or acute [42] beta-blocker therapy

- (iii) improving ventricular–large artery coupling by increasing the compliance of large arteries [32]
- (iv) decreasing the intra-organ arterial resistance (and therefore increasing intra-organ flow) by decreasing Pcc.

It is also possible that inodilators might exert potential harmful effects through:

- (i) decreasing Pms, thereby decreasing VR (and hence CO) with potential activation of the baroreflex; this could occur in the absence of corrective measures such as increase of Vs by volume expansion
- (ii) indirect positive chronotropic effect: this is the most likely explanation of the absence of beneficial effects of levosimendan in patients with heart failure observed in the SURVIVE study [29].

Finally, it is possible that the ratio of positive inotropism (and the mechanism of the positive inotropic effect) versus vasodilation could explain the results of meta-analyses. For instance, it is plausible that the lack of beneficial effects of the PDE-III inhibitor milrinone in recent meta-analyses [3, 4] PDE-III is due to the fact that any gains from its undoubted positive inotropic effects [29] are eclipsed by the deleterious effects of increasing the calcium transient within cardiomyocytes. By contrast, levosimendan exerts positive inotropic effects via increasing the sensitivity of contractile proteins to calcium, has direct positive lusitropic effects [43] and probably has a more vasodilatory and organ-protective profile than milrinone through activation of adenosine triphosphate-dependent potassium channels [44–46]. These specific effects of levosimendan, as compared with inodilators such as milrinone, may explain why levosimendan has beneficial effects on survival in specific clinical situations, such as patients undergoing cardiac surgery or ICU patients [5–8].

To add to the complexity of regulation of the cardio-circulatory system in health and disease, frequently used interventions in the ICU, such as mechanical ventilation and drug-induced sedation, will alter the venous tone and VR as well as the compliance of large arteries [13, 14]. Furthermore, increased intra-abdominal pressure can increase the resistance of the hepatic vein, thus rendering the mobilization of the blood from the venous splanchnic reservoir ineffective.

Conclusions

It seems highly probable that the conceptual framework for haemodynamics should not be limited to the ‘cardiocentric’ view given the complexity of the physiology and pathophysiology of the cardiocirculatory system. The challenge, for the clinician, is to: (i) develop clinically validated monitoring tools for variables such as Pms or Pcc; (ii) establish therapeutic goals based on

such monitoring devices; and (iii) review therapy based on patient-specific effects of individual drugs and not on ‘statistical’ pharmacological effects. Our approach may explain why drugs such as levosimendan, effective both on cardiac contractility and on load, have a cutting edge over pure inotropes.

Conflict of interest

DL and XN do not declare any conflict of interest. PP is a full-time employee of Orion Pharma, where levosimendan, one of the drugs discussed in this article, was discovered and developed.

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List of abbreviations:

Csv — mean compliance of the venous system
 CO — cardiac output
 Ea — arterial elastance
 Ees — left ventricular elastance
 LV — left ventricular
 LVEF — left ventricular ejection fraction
 h — blood viscosity
 Pa — arterial pressure
 Pcc — critical closing pressure
 Pcv — central venous pressure
 PDE — phosphodiesterase
 Pms — mean systemic pressure
 Pra — right atrial pressure
 Pv — venous pressure
 Rven/Vres — venous resistance
 SNS — sympathetic nervous system
 SVR — systemic vascular resistance
 VR — venous return
 Vs — stressed blood volume
 Vt — total blood volume
 Vu — unstressed blood volume

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