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REVIEW

Revisiting the relationship between left ventricular ejection fraction and ventricular–arterial coupling

Serban Mihaileanu[1] and Elena-Laura Antohi[2,3]*

[1]*Institut Mutualiste Montsouris, Paris, France;* [2]*Emergency Institute for Cardiovascular Diseases 'C.C. Iliescu', Bucharest, Romania;* [3]*University for Medicine and Pharmacy 'Carol Davila', Bucharest, Romania*

Abstract

The aim of this article was to analyse in-depth the relationship between left ventricular (LV) ejection fraction (EF) (LVEF) and the most commonly used formulas for the calculation of LV elastance (Ees), volume intercept at 0 mmHg pressure (V0), effective arterial elastance (Ea), and ventricular–arterial coupling (VAC) as are validated today. We analyse the mathematical resulting consequences, raising the question on the physiological validity. To our knowledge, some of the following mathematical consequences have never been published. On the basis of studies demonstrating that normal LV dimensions and LVEF have a Gaussian unimodal distribution, we considered that the normal modal LVEF is 62% or very close to it. Expressed as a fraction, it is 0.62, that is, the reciprocal of the Phi number (namely, $1/\Phi$ 0.618). Applying Euclid's mathematical law on the extreme and mean ratio (the golden ratio), we studied the LVEF–VAC relationship in normal hearts. The simplification of the VAC formula (with V0 = 0) leads to false physiological results; V0 extraction from single-beat Chen's formula leads to high negative results in normal subjects; based on the Euclid law, LVEF and Ea/Ees will be equal for a ratio value of 0.618 (62%) where V0 cannot be different from 0 mL; LVEF and VAC inverse relationship formula (Ea/Ees = 1/LVEF $-$ 1) is reducible to a fundamental property of Phi: $1/\Phi = (\Phi - 1)$, being valid only if LVEF = VAC at a 0.618 value; according to this restriction, Vo can only be 0 mL, thus describing a very limited range**.** The Ea/Ees ratio, owing to its mathematical more dynamic behaviour, can be more sensitive than LVEF, being a valuable clinical tool in patients with heart failure (HF) with reduced EF, acute unstable haemodynamic situations, where Ees and Ea variations are disproportionate. However, the application is doubtful in HF with preserved EF where Ees and Ea may have same-direction augmentation. The modified VAC formula suffers from oversimplification, reducing it to a dimensionless ratio, which is supposed to approximate non-linear time-varying functions. Thus, we advocate for caution and in-depth understanding when using simplified formulas in clinical practice.

Keywords Left ventricular ejection fraction; Ventricular–arterial coupling; Left ventricle elastance; Effective arterial elastance; Phi number

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**Correspondence to: Antohi Elena-Laura, Emergency Institute for Cardiovascular Diseases 'C.C. Iliescu', Sos. Fundeni, 258, sect 2, Bucharest 024102, Romania. Tel: +40744665208. Email: laura.antohi@gmail.com*

Introduction

Ventricular–arterial coupling (VAC) is considered as the cornerstone of the functional relation between ventricles and the arterial system. VAC is defined by the ratio between effective arterial elastance (Ea) and left ventricular (LV) elastance (Ees). Thus, VAC = Ea/Ees is key to understanding heart failure with reduced ejection fraction (HFrEF), but arguable for patients with heart failure with preserved ejection fraction (HFpEF). The aim of this brief review is to draw attention on the mathematical consequences when using some common formulas. Incomplete answers to some questions remain: whether the LV ejection fraction (LVEF) and VAC relationship reflect a physiological truth or just a mathematical issue, and whether the calculation of both VAC and LVEF may provide richer haemodynamic information than LVEF alone and in what kind of situation.

Non-invasive single-beat LV Ees can be calculated by several approaches. The Chen *et al*. formula,[1] which is the most often used, is calculated on the basis of systolic and diastolic blood pressure, stroke volume, LVEF, pre-ejection time, and total ejection time. As to make a feasible ratio between Ees and Ea, using the same units for the numerator and denominator, Sunagawa *et al*.[2] in dogs and Kelly *et al*.[3] in humans

demonstrated the efficiency of a highly simplified formula of Ea, called effective arterial elastance.

$$\mathrm{VAC} = \frac{\mathrm{Ea}}{\mathrm{Ees}} = \frac{\frac{\mathrm{ESP\ (mmHg)}}{\mathrm{SV\ (mL)}}}{\frac{\mathrm{ESP\ (mmHg)}}{\mathrm{ESV\ -\ Vo\ (mL)}}},$$

where ESP is the end-systolic LV pressure; ESV, end-systolic LV volume; SV, stroke volume; and Vo, theoretical LV volume at o mmHg pressure.

Some authors used the reciprocal ratio for VAC: $\frac{\mathrm{Ees}}{\mathrm{Ea}}$.[4,5] Even if the simple Ea formula is highly correlated to the arterial load, it is not identical and does not take into account strong determinants such as the reflected wave or the heart frequency. A recent detailed report on the advantages and disadvantages of using Ees and Ea formulas for VAC calculation was published in a consensus document by Ikonomidis *et al*.[6] It has to be stressed that the non-invasive single-beat formulas are steady-state linear extrapolation, based on a single pressure–volume point, approximating non-linear time-varying functions.

V0 is an extrapolated value, representing the unstressed LV volume intercept of the volume axis at a theoretical end-systolic pressure of 0 mmHg. Its value can be either positive or negative.

In normal hearts, V0, as estimated by invasive studies, is close to 0 mL. Furthermore, Vo is approximated to be 0 mL in many studies for non-enlarged, non-remodelled left ventricles.[7] Invasive studies in normal subjects demonstrated mean V0 values close to 0 mL: Starling,[4] V0 = 1 ± 23 mL; Maughan *et al*.,[8] V0 = 5.5 ± 1.0 mL; Senzaki *et al*.,[9] V0 = between +2.1 and −3.14 mL; and Asanoi *et al*.,[10] V0 = 4 mL/m^2 (between −10 and +26 mL). However, even if the mean value for the normal subjects is near 0 mL, inside the groups, there are high individual variations.

As the end-systolic pressure–volume curves are non-linear and time varying, with a different shape according to the contractile status, Ees and V0 intercept covary.[11] This may explain the important variations inside the same group of patients—V0 extrapolation from one single point leading therefore to approximations. What seems clear is that V0 will be around 0 mL in a strictly normal LV, highly positive in a dilated remodelled LV, and probably rather negative in a small concentric remodelled LV working at high energy demands.

Comparing left ventricular ejection fraction and ventricular–arterial coupling

Each of these two ratios refers to a dimensionless metric. When comparing them, the overlapping results may lead to equivocal understanding. The VAC simplification to a volumetric ratio is misleading and should be avoided except for the particular situation when V0 = 0 mL: $\frac{\mathrm{Ea}}{\mathrm{Ees}} = \frac{\frac{\mathrm{ESP\ (mmHg)}}{\mathrm{SV\ (mL)}}}{\frac{\mathrm{ESP\ (mmHg)}}{\mathrm{ESV\ -\ Vo\ (mL)}}} = \frac{\mathrm{ESV\ -\ Vo\ (mL)}}{\mathrm{SV\ (mL)}}$. It is observable that after the common factor ESP was cancelled, the numerator and denominator are inverted, giving, therefore, Vo an opposite meaning: the greater the Vo will be, the lower the VAC, which is false. Simplified or not, the result is the same. Transforming the Ea/Ees ratio into $\frac{\frac{\mathrm{ESP\ (mmHg)}}{\mathrm{SV\ (mL)}}}{\frac{\mathrm{ESP\ (mmHg)}}{\mathrm{ESV\ -\ Vo\ (mL)}}}$ leads to a specious result, suggesting that ESV, Vo, and SV could be considered as independent values. Apparently, a Vo positive variation may lower (meaning improve) the VAC. ESV and Vo have a tendency to increase with the dilation/remodelling and altered contraction of the LV. SV is expected to vary with the ESV–Vo modification. With three constituents, each intimately linked to the other, it is hardly conceivable to consider any independent variation; it is best to consider a global covariation. VAC should be formulated by the Ea and Ees ratio, each of them being individually calculated.

The extreme reduction of this ratio, when V0 = 0 mL, leads to a physiologically interesting proportion: $\frac{\mathrm{ESV\ (mL)}}{\mathrm{SV\ (mL)}}$, but too simplistic for the coupling definition.

LVEF and VAC can be expressed as a ratio of elastances. LVEF formula can be rewritten in a way where all the components of the numerator and denominator are expressed in terms of elastances (Appendix A.1).

Therefore, the LVEF formula $(\frac{\mathrm{SV}}{\mathrm{EDV}})$ can be developed to $\frac{\mathrm{ESP}*\mathrm{Ees}}{\mathrm{ESP}(\mathrm{Ea}+\mathrm{Ees})+\mathrm{Ea}*\mathrm{Ees}*\mathrm{Vo}}$.

This way of looking at the LVEF demonstrates that LVEF can be regarded as the result of the two elastances interplaying.

Finally, when V0 = 0 mL, the ratio will simplify to

$$\mathrm{LVEF} = \frac{\mathrm{ESP}*\mathrm{Ees}}{\mathrm{ESP}(\mathrm{Ea}+\mathrm{Ees})+\mathrm{Ea}*\mathrm{Ees}*\mathrm{Vo}} = \frac{\mathrm{ESP}*\mathrm{Ees}}{\mathrm{ESP}(\mathrm{Ea}+\mathrm{Ees})} = \frac{\mathrm{Ees}}{\mathrm{Ea}+\mathrm{Ees}},$$

where ESP is the end-systolic LV pressure and Vo is the theoretical LV volume at o mmHg pressure.

This way of considering LVEF indicates a direct relation to Ees (as numerator) and inverse to Ees + Ea (as denominator). This implies the mathematical weight of Ea compared with Ees: for an LVEF at 0.55, Ees needs to be 1.22 times (11/9) greater than Ea, while for an LVEF at 0.65, it needs to be 1.86 greater (13/7). Let us imagine a small concentric remodelled LV working at an LVEF of 0.7: Ees needs to be 7/3 greater than Ea (2.3 * Ea). In order to increase the LVEF by 5 points at 0.75, during exercise, in the ratio Ees/Ea, Ees needs to be three times greater than Ea (Ees = 3 * Ea), which

is physiologically hard to achieve if Ea does not decline in parallel—explaining therefore the blunting effect exerted by the Ea on LVEF, when it does not decrease or even augment at physical effort. This explains why LVEF, being a normalized ratio of Ees and Ea, is not a reliable contractility discriminator but should be considered as a composite result of Ees and Ea, being therefore an excellent clinical predictor.

V0, called also the intercept value, is the discriminant element between the pressure–volume relation and Ees, as well as between LVEF and VAC.

Can V0 be extracted from the Chen or other single-beat Ees formulas? Nothing is less certain. He *et al*.,[12] in a non-invasive study of 357 subjects, obtained high negative V0 results in all normals but also in mildly decreased LVEF patients. A possible explanation is presented in Appendix A.2.

As long as V0 is 0 mL, in normal hearts, LVEF is preload insensitive for a wide range of preloads,[13] while the VAC will react to any SV variation. In chronic overload, for example, in compensated mitral regurgitation, LVEF is normal as far as V0 = 0, but once the LV remodelling occurs, V0 will increase, accompanying a diminished LVEF.

V0 has a very important prognostic value. When V0 = 0 mL, the LVEF–VAC relationship is less interesting, being composed of two reciprocal mathematical derivatives. On the contrary, when V0 ≠ 0 mL, and it becomes a powerful discriminating criterion, its augmentation coming along with LV function degradation. Ky *et al*.[14] demonstrated in a large cohort of patients with HFrEF that EDV, V0, V100, and VAC are associated with prognosis. Similar to V0, but not virtual, V100 has the same meaning being the calculated LV systolic volume at 100 mmHg pressure. Intercepting the pressure axis at higher levels than 0 mmHg leads to less volume variation and excludes the negative values. Narayan *et al*.[15] in the PREDICT Study found that changes in longitudinal strain rate, V100, and Ea were individually predictive of cancer therapeutics (anthracycline)-related cardiac dysfunction.

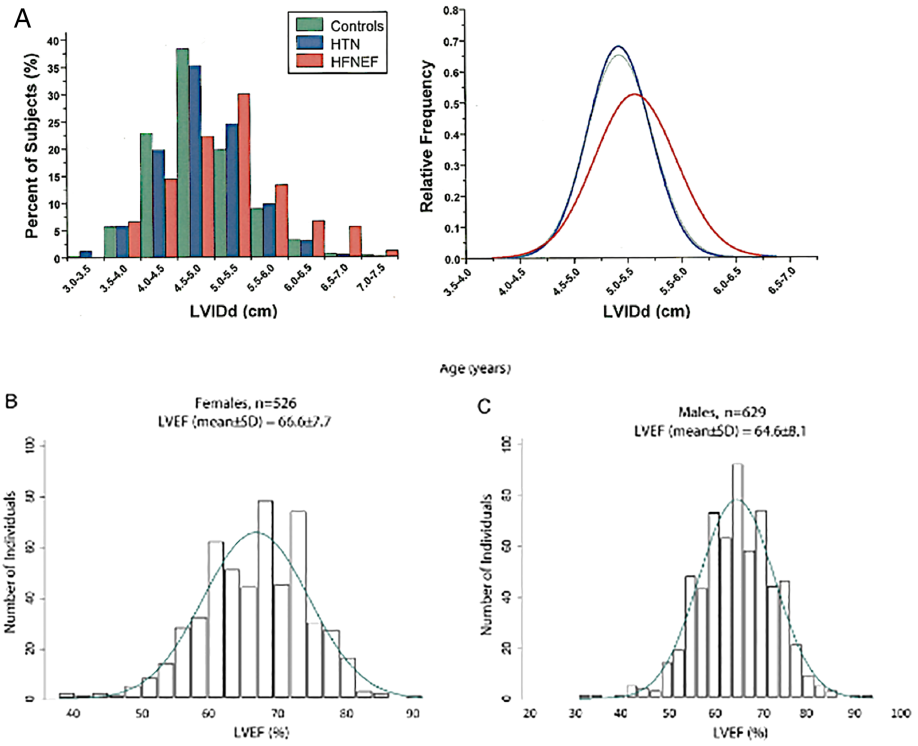
Ventricular–arterial coupling variations are mathematically more sensitive than left ventricular ejection fraction variations

For an LVEF variation from 0.55 to 0.65 (+18%) approximating V0 = 0 mL, VAC will have a much higher negative variation of −34% (if VAC = Ea/Ees) or even more as a positive variation +52%, if VAC is calculated as Ees/Ea. Intensive care units as well as anaesthesiology facing unstable haemodynamic situations with VAC uncoupling, as cardiogenic or septic shock, post-operative acute heart failure, and also stress echocardiography can better discriminate by the VAC calculation between LV contractile status and periphery. Morelli *et al*.[16] demonstrated in patients with septic shock that diminishing heart frequency with esmolol decreased Ea without modifying LVEF. The difference between flow reserve and contractile reserve is a concept derived from Ees and Ea calculation. In chronic situations, subtle Ea and/or Ees variations can lead or not to a significant variation of the VAC without any modification of the LVEF. As an example, Lekavich *et al*.[17] demonstrated in a retrospective study cohort of patients with HFpEF matched against controls a significant difference in VAC (P = 0.0001), while LVEF was quite identical. Inversely, Borlaug *et al*.[18] in a very large sample of patients did not find any difference in LVEF or VAC by comparing normal subjects with hypertensive and HFpEF patients. Meanwhile, Ea and Ees were both significantly augmented, but in a such a proportion that they did not affect the VAC ratio. Borlaug and Kass made an important statement: 'Perhaps more important than the coupling ratio of ventricular and vascular stiffness are their absolute values',[19] which seems to be the core situation in the HFpEF. Therefore, in HFpEF, the Ea/Ees as a dimensionless ratio (VAC) may have a less predictive value than Ees and Ea taken separately. Looking at the dimensionless aspect of the LVEF, where the metric cannot express the magnitude of ESV and EDV, Kerkhof *et al*.[20] proposed as a fundamental approach a 'volume regulatory state diagram in terms of ESV versus EDV as a cornerstone for more insightful analysis of ventricular function', linking therefore the LVEF to its constituents.

Left ventricular ejection fraction–ventricular–arterial coupling relationship in normal left ventricles

Echocardiographic studies (M mode, 2D, or 3D) demonstrated a statistically Gaussian pattern of the distribution of the LV dimensions in normal individuals[21–23] (*Figure 1A*). LVEF in normal subjects has the same normal statistical distribution. The normal distribution rate of the LVEF in 91 healthy subjects[25] had a unimodal Gaussian distribution, with a mean value of 61.2%. Gebhard *et al*.[26] found a mean LVEF of 62 ± 0.5% in young women and a similar 62 ± 0.5% in young men in a large retrospective 2D echocardiography study population of 5307 normal subjects. The group demonstrated a significant increase in LVEF with age, more pronounced in women. Lang *et al*.[27] quoted four studies by 3D echocardiography, totalling 1780 subjects. Among 10 subgroups (male or female, white or Indian), eight had a mean LVEF of between 61% and 62%. In 1200 normal subjects, Pfisterer *et al*. by nuclear cardiology[28] found the weighted mean normal values for LVEF at rest to be 62.3 ± 6.1%. The CONFIRM registry[24] found on 1155 normal subjects a unimodal Gaussian distribution of CT computed LVEF, with a mean value of 62.9% in young men and 64.7% in young women (*Figure* 1B). This

FIGURE 1 (A) With permission from Maurer *et al*. Normal statistical distribution of LV diastolic dimensions. Controls, normal subjects; HTN, hypertension; and HFpEF, heart failure with preserved ejection fraction. All three groups have a Gaussian distribution, where mean, modal, and median values are superposed.[22] (B) With permission from Gebhard *et al*. The CONFIRM Study: Gaussian unimodal distribution of the left ventricular ejection fraction (LVEF) in women and men. Computed tomography (CT)-generated ejection fraction (EF) data are often slightly higher than those based on echocardiography.[24]



registry confirmed again the significant gender and age differences: higher in women and the elderly.

A normal Gaussian distribution implies that the modal (most expected value), mean, and median values are the same, resulting in that the mean normal value of the LVEF is also the modal value—being therefore the most expected value. It appears, therefore, that an LVEF value at ~62%, has a high probability to be the modal value, or very close to it in normal young subjects.

Interestingly, Wehner *et al*.[29] on a very large number of patients demonstrated that the overall, adjusted hazard ratios for mortality had a U-shaped relationship for LVEF with a nadir of risk at an LVEF of 60–65%, which also supports the idea that the optimal LVEF is somewhere near to 62%. The VAC was not calculated.

Comparing left ventricular ejection fraction with ventricular–arterial coupling in normal hearts

For mathematical reasons, LVEF will be expressed in decimals, for example, 0.62 instead of 62%. Both LVEF and VAC formulas contain the same two elements: Ea and Ees or SV and ESV (Appendix A.1). Comparing one with the other is like comparing $\frac{a}{a+b}$ with $\frac{b}{a}$. For a LVEF measured at 0.618 (≈62%), this relationship will listen to the Euclid mathematical law on the extreme and mean ratio[30] being expressed as follows: If $\frac{a+b}{a} = \frac{a}{b}$, then the result is $\frac{1+\sqrt{5}}{2}$, being abbreviated as Phi (Φ) and approximated at ≈1.618033988749894848, etc. Phi is an irrational number (like π) with unique properties: one of them, which will be recalled later, is its reciprocal value, where $1/\Phi = \Phi - 1 \approx 1.618 - 1 = 0.618$. As a simple mathematical application, according to the Euclid law, every time the reciprocal ratio of Phi, $\frac{a}{a+b}$ (instead of $\frac{a+b}{a}$), will reach the value of $1/\Phi$, it will be equal to $\frac{b}{a}$ (instead of $\frac{a}{b}$), becoming $\frac{a}{a+b} = \frac{b}{a} = \frac{1}{\Phi} = 0.618$.

Phi proportions are frequently encountered in nature and in the human body. Later, in the Middle Ages, this mathematical rule was called the golden ratio.

It is understandable why if the LVEF is 1/Φ (0.618 = 62%), the ratio $\frac{Ees}{Ees+Ea}$ listens to the mathematical law, becoming equal to the VAC formula: $\frac{Ees}{Ees+Ea} = \frac{Ea}{Ees} = \frac{1}{\Phi}$. Therefore, the relationship between Ees and Ea will be related to the common factor Phi and can be expressed as follows: Ees = Φ * Ea (1.618 * Ea) and Ea = Ees * 1/Φ (0.618 * Ees).

Another way to demonstrate the equality of LVEF and VAC for 0.618 is by simplifying the VAC ratio (Appendix A.3, 3a).

As a consequence of the equality of LVEF and VAC at 0.618, it is demonstrated, by a system of two equations, that V0 cannot be else than 0 mL (Appendix A, 4a and 4b): For this value of LVEF and VAC, Ees and Ea will be related by the golden ratio rule: Ees = Φ * Ea (approximate form: Ees = 1.61803 * Ea). For the simplified form, the relation between ESV and SV will be: SV = Φ * ESV.

For practical means, it results from the simplified formula of VAC that when SV = Φ * ESV, the value of VAC cannot be other than 1/Φ, and V0 will be 0 mL.

In summary, V0 can be mathematically considered 0 mL, in the following situations: normal non-remodelled LV with an LVEF at 0.62 or LVEF = Ees/(Ees + Ea). V0 will also be 0 mL for the following golden ratio-related formulas: Ees = Ea * Φ or SV = Φ * ESV.

Gayat *et al*.[31] by 3D echocardiography obtained an LVEF of 0.62 and a VAC value at 0.6 (1/Φ). Migliore *et al*.[32] obtained in asymptomatic aortic stenosis patients a mean VAC value of 0.61 for an LVEF of 0.62.

Starling's work[4] in 22 normal subjects found an Ees/Ea ratio of 1.62 (the value of Φ) for a mean V0 close to 0 (+1 mL). Bombardini *et al*.[5] found by echocardiography in normal subjects a mean LVEF of 0.61 for a VAC of 1.6. Yetkin *et al*.[33] demonstrated in normal hearts that the ratio of the LV diastolic to systolic diameters is 1.614, quite identical to the Φ number. Henein *et al*.[34] calculated the ratio of the vertical to transverse cardiac diameters at ~1.618 in normal subjects, despite ethnic differences. Kerkhof *et al*.[35,36] indicated that 1/Φ approximated at 0.62 comes close to the normal value of LVEF.

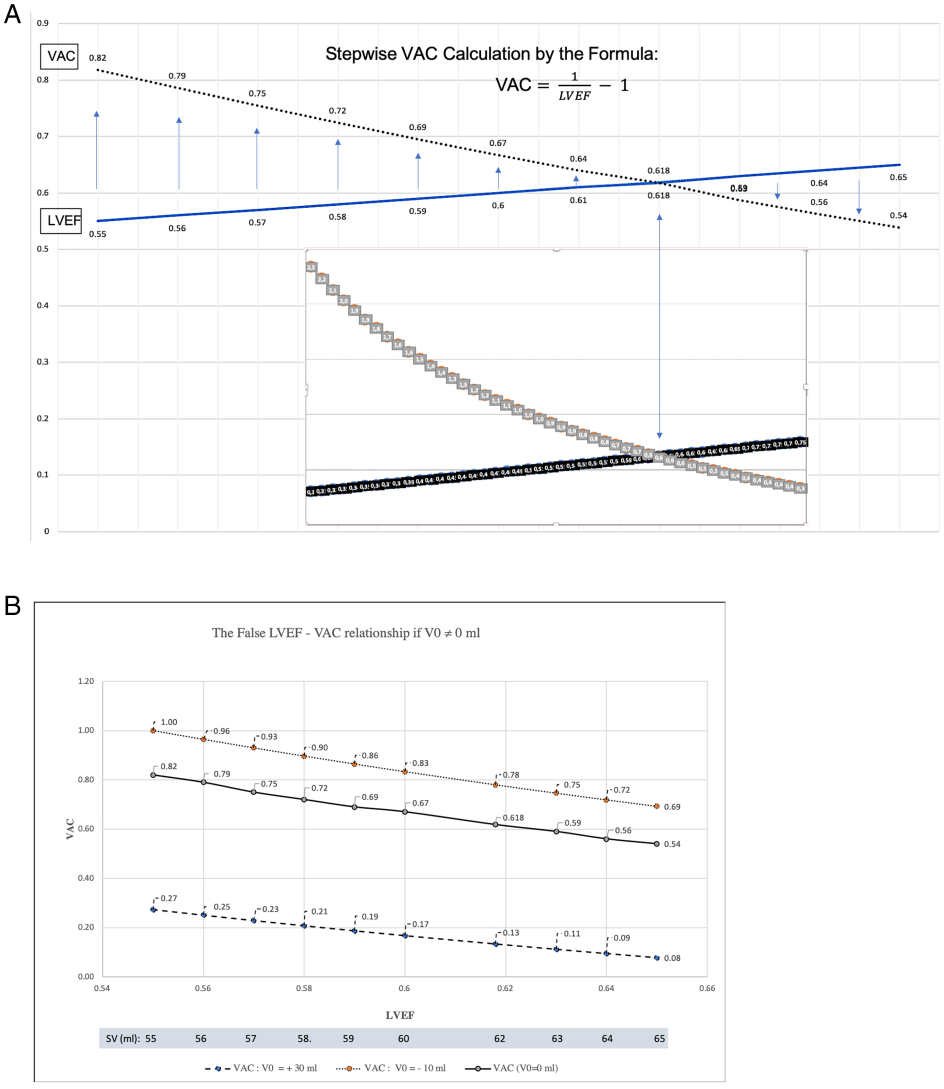
The mathematical formula defining the inverse relationship between LVEF and VAC is expressed as Ea/Ees = 1/LVEF − 1 or as its reciprocal formula LVEF = 1/(1 + Ea/Ees) being often cited in the literature.[7,37–40] As a general statement, this equality is valid only when V0 = 0 mL (Appendix A.3, 3b).

When LVEF is 0.618 (62%), this formula is ruled by the Phi number properties. It was demonstrated that for an LVEF of 0.618 ($\frac{1}{\Phi}$), Ea/Ees cannot be other than 0.618. For this value, the formula can be rewritten as $\frac{1}{\Phi} = \frac{1}{1} - 1$ and then simplified to $\frac{1}{\Phi} = \Phi - 1$, describing therefore the already cited fundamental property of the Phi number: 1/Φ = Φ − 1 ≈ 1.618 − 1 = 0.618.

Related by this formula, LVEF and VAC have a curvilinear divergent relation, with a crossing point at $\frac{1}{\Phi}$(0.618) where VAC and LVEF are equal (*Figure 2A*), supporting therefore that the modal value of normal VAC and LVEF distribution should be 0.618. Beyond the mathematical truth, does this formula reflect a physiological reality? As it is frequently seen, the golden ratio reflects an optimal natural situation, and in this case, it depicts the LVEF and VAC equality, in normal hearts, when V0 is ideally at 0 mL. Remoteness from the LVEF/VAC curves crossing point, to the left or to the right, suggests a non-measurable physiological abnormality, because V0 ≠ 0 mL, having an unknown value. For the LVEF normality interval (0.55 to 0.65), the corresponding VAC normality interval should be 0.82 to 0.54. For a larger LVEF normality interval, from 0.5 to 0.65, including an ambiguous LVEF grey zone between 0.55 and 0.5, the VAC normality interval is calculated between 1 and 0.54. Normal VAC value[6] based on an invasive study in humans[41] is considered 1.0 ± 0.36. If we should use the formula Ea/Ees=1/LVEF – 1 this range becomes impossible for the normal physiology, because a VAC ratio > 1 would correspond to an LVEF < 0.5, which is the decoupling point. The false VAC–LVEF relationship when V0 ≠ 0 mL is demonstrated in *Figure* 2B. Dilated, remodelled hearts with poor LV function represent the conditions associated with an increase of the V0 value—exactly the opposite of what is depicted in *Figure* 2B. A possible explanation is that this formula demonstrates no more than a Phi number property found in the normal-optimal LVEF–VAC relationship being physiologically true only for a narrow interval around the 0.62 value; therefore, its clinical use should be reconsidered.

A question must be raised: When using the actual formulas, is the VAC calculation a valuable clinical tool? It was chosen to express the VAC, like the LVEF, as a dimensionless ratio, meaning comparing nude numbers. This way was rather successful in HFrEF because V0 is generally elevated, but it has led to a non-discriminative impasse in HFpEF where both of them can show normal values while Ees and Ea are modified. So closely related to the LVEF, which can be somewhere in the middle of the normality range, the VAC calculation will also give normal values. It was demonstrated that the variation of Ea and/or Ees will result in a much higher variation of the VAC while LVEF variation will be significantly less. This more dynamic VAC responsiveness has a clear clinical interest in HFrEF, cardiogenic or non-cardiogenic shock, unstable haemodynamics, and/or acute or chronic therapeutic intervention as well as for pharmacological or stress tests. On the other hand, it has to be mentioned that the simplistic way to define Ea is far from the pathophysiology of HFpEF[40] explaining, at least partially, the VAC calculation clinical

FIGURE 2 (A) Ventricular–arterial coupling (VAC) and left ventricular ejection fraction (LVEF) related by the formula VAC = 1/LVEF − 1 (LVEF, solid line, normal values, between 0.55 and 0.65; VAC, dotted line, calculated values (arrows), for each LVEF 0.01 stepwise increment within the interval 0.55–0.65). Ordinate, LVEF value and the derived VAC result; abscissa, VAC calculation for each step increment of the LVEF. The divergent relation has a crossing point at 0.618, where the equality is true and Vo = 0 mL. For its immediate vicinity, a linear relation could be approximated. Wider LVEF intervals (small box) demonstrate only a trend of LVEF-to-VAC calculation formula, where VAC has a curvilinear aspect relative to the linear LVEF variation. No strict relationship can be considered—this formula is valid only for Vo = 0 mL. The crossing point and its immediate vicinity represent the ideal normal values. Patients with HFrEF and elevated VAC will be found when moving to the left, away from the crossing point and the normal values. To the right of the crossing point, the interval is much smaller and might contain small concentric remodelled LV cavities in hypertensives with elevated LVEF or eventually patients with HFpEF. (B) False VAC–LVEF relationship, by considering non-zero values for Vo in Ees = ESP/(ESV − Vo); for the equality, Ea/Ees = 1/LVEF − 1. Adding +30 mL to Vo produces a huge shift of the VAC, near to 0 values, while adding −10 mL to Vo will give an upward shift—both situations being contrary to the meaning of the Vo variations. Solid line, Vo = 0 mL; dotted line, Vo = +30 mL; pointed line, Vo = −10 mL.



uncertainty for this condition. Both Ees and Ea are steady-state formulas, trying to depict time-varying non-linear functions.

Ea/Ees ratio suffers from its possible degrading to the simple volumes, which define the LVEF. Looking from the point of view of these formulas, V0 appears as the only discriminant factor between LVEF and VAC, but it cannot be correctly extracted from the single-beat Ees formulas—meaning that one single pressure–volume point cannot draw a non-linear time-varying function. Extracting from a single-beat Ees formula, instead of V0 a V at higher pressure such as V30 and V100, by reducing the extrapolation line, offers less odd values. Comparing, but transforming VAC into LVEF or inversely, opens the door to oversimplification, leading to a dimensionless ratio contest, often with odd results—Ees and Ea provide richer information. At the same time, the simplified

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Ea formula ($\frac{\text{ESP (mmHg)}}{\text{SV (ml)}}$) is another caveat for the VAC formula. VAC, as a relation between heart and periphery, is an essential concept; should we renounce or improve its calculation? How do we escape the oversimplification?

Gayat *et al.*[31] demonstrated in normals versus dilated cardiomyopathy patients that Shishido's single-beat Ees formula (more difficult for daily practice) has a superior discriminate power over the Chen formula.

In conclusion, as long as we use simple formulas based on dimensionless ratios and linear relations, there is a risk of mathematical rules taking over the physiology. We demonstrate that for normal hearts, the LVEF and Ea/Ees will be equal at 0.618 (62%) and V0 will be 0 mL—both Ees and Ea being related by the common factor Phi. At the same time, for this value, the LVEF and VAC inverse relationship formula is reduced to a fundamental property of the Phi number, being true only when V0 = 0 mL. The Ea/Ees ratio, owing to its more dynamic behaviour, with greater variations than the LVEF, is still a valuable clinical tool in patients with HFrEF and/or acute unstable haemodynamic situations; on the contrary, it appears doubtful for patients with HFpEF. The fundamental relationship between the heart and periphery expressed by the VAC is today underused, because of the tendency to reduce it to a volumetric ratio, losing therefore its fundamental meaning. Efforts have to be done to save it from oversimplification and improve the concept of VAC so as to increase its clinical utility.

Conflict of Interest

None declared.

Appendix A.

A.1Calculation of LVEF in terms of elastance

$$\text{LVEF} = \frac{\text{SV}}{\text{EDV}} = \frac{\text{SV}}{\text{SV} + \text{ESV}},$$

where SV and ESV can be expressed by Ea and Ees, as follows:

$$\text{If Ea} = \text{ESP}/\text{SV, then SV} = \text{ESP}/\text{Ea}.$$

$$\text{If Ees} = \text{ESP}/(\text{ESV} - \text{Vo}), \text{ then ESV} = \text{ESP}/\text{Ees} + \text{Vo}.$$

$$\text{LVEF} = \frac{\frac{\text{ESP}}{\text{Ea}}}{\frac{\text{ESP}}{\text{Ea}} + \frac{\text{ESP}}{\text{Ees}} + \text{Vo}} = \frac{\text{ESP}*\text{Ees}}{\text{ESP}(\text{Ea} + \text{Ees}) + \text{Ea}*\text{Ees}*\text{Vo}}.$$

$$\text{If Vo} = 0, \text{ then LVEF} = \frac{\text{Ees}}{\text{Ees} + \text{Ea}}.$$

A.2V0 extraction starting from the Chen formula may lead to doubtful results

$$\text{Ees} = \frac{\text{ESP}}{\text{ESV} - \text{Vo}} \rightarrow \text{Vo} = \frac{\text{Ees}*\text{ESV} - \text{ESP}}{\text{Ees}}, \text{ or Vo} = \text{ESV} - \frac{\text{ESP}}{\text{Ees}}$$

V0 will be 0 mL or positive only if $\text{ESV} \geq \frac{\text{ESP}}{\text{Ees}}$, meaning a rather high ESV!

This explains the pronounced tendency for negative V0 results.

Clinical example for a strictly normal subject:

If ESV = 30 mL, ESP = 100 mmHg, and Ees = 1.6 mmHg/mL, then $\text{V0} = 30 \text{ mL} - \frac{100 \text{ mmHg}}{1.6 \text{ mm g/mL}} = -32.5 \text{ mL}$.

Therefore, V0 cannot be 0 mL, unless for a very large LV, where

$$\text{ESV} = \frac{100 \text{ mmHg}}{1.6 \text{ mmHg/mL}} = 62.5 \text{ mL}.$$

A.3The equality of LVEF and VAC to the value of 0.618 starts by simplifying the VAC ratio

(**3a**) $\text{If LVEF} = \frac{\text{SV}}{\text{EDV}} = \frac{\text{SV}}{\text{SV} + \text{ESV}} = 62\% \text{ (0.618)} = \frac{1}{\Phi}$.

And VAC is simplified to $\frac{\text{ESV}}{\text{SV}}$.

Then $\frac{\text{SV}}{\text{SV}+\text{ESV}} = \frac{\text{ESV}}{\text{SV}}$, if one of the two ratios reaches the value of $\frac{1}{\Phi}$, according to Euclid's theorem.

(**3b**) The equality $\frac{\text{Ea}}{\text{Ees}} = \frac{1}{\text{LVEF}} - 1$ is transformed in its constituents:

$$\frac{\frac{\text{ESP}}{\text{SV}}}{\frac{\text{ESP}}{\text{ESV} - \text{Vo}}} = \frac{1}{\frac{\text{SV}}{\text{SV} + \text{ESV}}} - 1.$$

The equality is then simplified to $\frac{\text{ESV} - \text{Vo}}{\text{SV}} = \frac{\text{ESV}}{\text{SV}}$, where Vo cannot be other than 0 mL.

(**4a**) Solving a system of two equations, when LVEF and VAC are equal at 0.618.

a. $\text{LVEF} = \frac{\text{ESP}*\text{Ees}}{\text{ESP}(\text{Ea} + \text{Ees}) + \text{Ea}*\text{Ees}*\text{Vo}}$, and $\text{VAC} = \frac{\text{Ea}}{\text{Ees}}$.

b. $\frac{\text{ESP}*\text{Ees}}{\text{ESP}(\text{Ea} + \text{Ees}) + \text{Ea}*\text{Ees}*\text{Vo}} = \frac{\text{Ea}}{\text{Ees}} = \frac{1}{\frac{1+\sqrt{5}}{2}} = \frac{1}{\Phi} = 0.618.$

c. $\text{Ees} = \text{Ea} * \frac{1+\sqrt{5}}{2}$.

d. Replace Ees by Ea * $\frac{1+\sqrt{5}}{2}$.

e. $$\frac{ESP*Ea*\frac{1+\sqrt{5}}{2}}{ESP\left(Ea+Ea*\frac{1+\sqrt{5}}{2}\right)+Ea*Ea*\frac{1+\sqrt{5}}{2}*Vo}=\frac{1}{\frac{1+\sqrt{5}}{2}}.$$

f. For this equality, V0 = 0 mL and Ees = Ea * Φ.

(**4b**) Solving a system of equations with the simplified formula of VAC:

a. LVEF = $\frac{SV}{SV+ESV}=\frac{1}{\frac{1+\sqrt{5}}{2}}$ and VAC= $\frac{ESV-Vo}{SV}=\frac{1}{\frac{1+\sqrt{5}}{2}}$, where $\frac{1}{\frac{1+\sqrt{5}}{2}}\approx 0.618$.

b. Applying the Euclid theorem:

$$\text{If } \frac{SV}{SV+ESV}=\frac{ESV-Vo}{SV}=\frac{1}{\frac{1+\sqrt{5}}{2}}=\frac{1}{\Phi},$$

then $\frac{SV}{SV+ESV}=\frac{ESV}{SV}$. It results in the following:

$$Vo = 0 \text{ mL and } SV=\frac{1+\sqrt{5}}{2}*ESV,$$

where $\frac{1+\sqrt{5}}{2}=\Phi$, and LVEF is the left ventricle ejection fraction; ESP, end-systolic LV pressure; SV, stroke volume; EDV, end-diastolic LV volume; ESV, LV end-systolic volume; Vo: LV theoretical volume at 0 mmHg pressure; VAC, ventricular–arterial coupling; Ea, arterial elastance; and Ees, ventricular elastance.

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