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INDICES FOR CARDIAC PERFORMANCE DERIVED FROM THE HEMODYNAMIC NON-INVASIVE AND INVASIVE EVALUATION IN PATIENTS WITH HEART FAILURE: ECHOCARDIOGRAPHIC AND CARDIAC CATHETERISM STUDY

DISSERTATION SUMMARY

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Dissertation Content:

General Part - Introduction

Heart failure (HF) remains a very frequent disease having an estimated prevalence of 8.52:1000 individuals, determining significantly elevated rates of invalidity and mortality together with high economic costs (1). Typically, HF patients are on a inexorable trajectory towards progressive deterioration, meaning acute episodes for severe symptom worsening/decompensation (sometimes requiring hospitalisation) alternating with calm periods - this classic trajectory having been described by Mihai Gheorghiade (2). Some structural and hemodynamic pathophysiological alterations occur before symptoms (i.e. acute myocardial injury, decrease in cardiac output and especially filling pressures elevation) or allow an excelent response tot neurohormonal and/or diuretic therapies and thus maintaining an asymptomatic good clinical status (2-4).

The parameters that are mostly used describe the cardiac performance remain left ventricular ejection fraction (LV EF) and ventricular-arterial coupling (VAC). Although their prognostic value and their ability to guide therapy is already taken for granted (5), LVEF has multiple limits that have been extensively described (6), but which have not been entirely incorporated in daily clinical practice.

Starting with the relationship described by Starling between sarcomere length and contraction force, Suga and Sagawa have shown that time variation of the instantaneous ratio between pressure and LV volume expresses the dynamics of LV intrinsec contractility independent from filling pressures (7). This time function defines myocardial stiffness and represents LV elastance (Ees): $Ees(t) = P(T)/(V(t)-Vo$. The very same authors - pioneers of cardiovascular hemodynamics, have created in a series of articles, the graphic representation of this variation during the cardiac cycle (which is known today as pressure-volume loop), and thus illustrating the effects of preload or afterload variation and integrating the concept of the relationship between LV pressure and volume at end-systole (8-10).

The ratio between effective arterial elastance (Ea) and ventricular elastance (Ees) define VAC and represent the interdependency between the LV and the peripheral circulation. Some authors (but this is less frequent) use the inverse ratio and define VAC as Ees/Ea.

The significance of VAC in HF is discussed of a simplified manner in one of the recent documents of the European Society of Cardiology (11), but it is especially relevant for the clinical practice in the critical care setting for both cardiogenic shock and non-cardiogenic shock (12,13). It has also been proven that VAC is correlated to plasmatic level of natriuretic peptides and has prognostic utility (14,15).

Accurate measurement of the VAC requires sophisticated invasive techniques using catheters specially destined for measuring the ventricular pressures and volumes (the techniques, methods and clinical utility have been revised in several documents, including the more recent Bastos article (16)).

Between the 1990's and 2000's several single beat formulas allowing the calculation of Ees and Ea have been developed (without requiring repetitive measurements and under hemodynamic interventions to describe pressure-volume loops) (17-24). These could be extrapolated for the non-invasive evaluations, using transthoracic echocardiography. The caveat of these formulas are that they are very complex (especially for Ees) and they extrapolate the value from a single cardiac cycle, assuming a linear relation.

VAC is optimal for the vales close to 1 (17,18).

IN HF with reduced EF, VAC will be significantly elevated - as a consequence of contractile depression (as expressed by Ees), and compensated by Ea elevation (19-21). The peripheral circulation has the capacity to compensate the LV contractility deficit and thus ensure an adequate coupling - this being a good prognosticator, even more so than Ees (15). One of the determining factors for VAC si V0. V0 represents the theoretical LV volume when pressure 0 mmHg. For the non-dilated normal heart, the estimated value for V0 using invasive studies is close to 0ml.This is why, we often encounter simplified formulas, that neglect the value of V0.

A significant work from Warriner et al. analysed the evolution of PV loop in parallel with HF progression through A to D stages, following HF patients with systolic LV dysfunction and excluding patients with HF preserved EF (23). Statistic analysis showed that from the hemodynamic point of view, there were no significant statistic differences between normals and HF stages A and B, just as there were no significant differences between stages C and D. Nonetheless, PVLs in normal individuals and in those in HF stages A and B were significantly different from the PVLs in patients with HF stages C and D, by the significant deterioration of Ees.

VAC in acute/chronic HF represents a critical parameter for the description of cardiac performance and a viable therapeutic target. The acceleration of development for therapeutical options in HF in the past few years, has brought back to focus the significance of hemodynamic alterations. The clinical evaluation of HF patients hemodynamics uses parameters that are too basic. The in-depth description of hemodynamic alterations in HF still remains a research topic, especially so for the non-invasive hemodynamics. The hemodynamic characterisation of HF patients is counted among the most important gaps in knowledge in the current document for the universal definition of HF (24).

Personal part

Research objectives:

This research was constructed in 4 separate studies that logically followed one after the other:

1. the theoretical analysis of the mathematical consequences when using simplified formulas for LVEF and VAC;
2. the comparison of different formulas for effective arterial elastance using invasive measurements; the evaluation of the accuracy of non-invasive measurements (by transthoracic echocardiography) as compared with direct standard invasive measurements (using left and right catheterise) for the simple, usual hemodynamic parameters;
3. pilot study to characterise the complex non-invasive hemodynamics of patients with advanced chronic HF with reduced LVEF as compared to a control group of asymptomatic patients;
4. the identification of surrogate simple to use non-invasive formulas, which would be accessible to clinical practice that would approximate essential hemodynamic parameters such as Ees and VAC in patients with chronic HF, using basic parameters that define the LV systolic function.

The research took place in the Emergency Institute for Cardiovascular Diseases "Prof.Dr. C.C.Iliescu", with the approval of its ethics committee, in patients that were evaluated clinically and using invasive and non-invasive methods, according to strictly routine indications - all patients signed an informed consent at admission and all data were anonymised.

II.1. The analysis of mathematical consequences using simplified formulas for VAC and LVEF

Simplified formulas for Ees and Ea are commonly used when reporting hemodynamic data. To establish an adequate protocol for the practical hemodynamic evaluation of HF patients, we theoretically analysed the mathematical consequences of the different formulas and the elements that may be eventually clinically integrated.

1.1. Phisiological limitations of simplified formulas for LVEF and VAC, when related by elastances.

Each of the 2 fractions represents a dimensionless number. Their values are expressed in rational numbers and can overlap which can lead to limited understanding. More than that, both fractions can be written in terms of elastances.

Using the mathematical formulas for Ea and Ees, respectively, VAC can be expressed as: VAC= Ea/Ees = ESP(mmHg)/SV (ml)/ ESP(mmHg)/ (ESV-V0) (ml) = (ESV-V0) (ml)/SV(ml) (ESP end-systolic pressure, ESV end-systolic volume, V0 theoretical volume for 0mmhg pressure, SV stroke volume).

Simplifying ESP would lead to a strictly volumetric ratio with limited meaning:

- the ratio could be adequately used only for the particular instance when V0=0ml (an acceptable approximation for normal hearts) when VAC is reduced to the ratio ESV (ml)/SV (ml); the ratio appears to be physiologically unlikely and too simplistic for the definition of VAC;
- on the other hand, when examining this ratio, the mathematical meaning of V0 when it is different from 0ml, becomes contrary to empirical data: the larger V0 will be (and as we previously stated, larger values have been calculated in patients with dilated hearts), the smaller the VAC will be (while for the remodelled LV with systolic disfunction, VAC is definitely elevated);
- calculating V0 starting from the different single beat formulas derived from non-invasive studies is questionable and leads to unlikely result:

  Ees= ESP/(ESV-V0) —> V0= (Ees*ESV-ESP)/Ees or V0= ESV- ESP/Ees.

  —> V0 will be either 0ml or positive only if ESV ≥ ESP/Ees, meaning significantly high ESV values!

1.2. VAC variations are mathematically more sensitive than LVEF variations.

For a LVEF variation between 0.55 and 0.65 (+18%) and approximating V0=0ml, VAC will have a negative variation much more significant of -34% (for the calculated VAC as the ‘classical’ ratio of Ea/Ees) or even more sensitive of +52% when it is calculated as the ratio Ees/Ea.

1.3. Comparing LEV and VAC in normal hearts.

Using simplified formulas and assuming V0=0ml, LVEF can be expressed in terms of elastances: LVEF=Ees/(Ees+Ea).

This will lead to the mathematical formula that expresses the relationship from the 2 parameters: VAC=Ea/Ees=1/FEVS – 1; this often expressed as FEVS=1/(1+Ea/Ees).

V0 can be considered mathematically equal to 0ml in the specific situation in which LVEF=0.62. When LVEF is 62% ≃0.618, meaning 1 / Φ, the ratio Ees/(Ees+Ea) is a subject of Euclid’s mathematical law, and thus becoming equal to the formula VAC= Ees/(Ees+Ea)=Ea/Ees= 1/Φ=0.618.

In this way, the relationship between Ees and Ea will be governed by the Phi number: Ees = Φ * Ea (=1.618*Ea). This mathematical equality between LVEF and VAC is only possible for the 0.618 value and for V0 =0ml - as it results from solving a complex equation system. This is the physiological condition of non-dilated, normal hearts.

1.4. LVEF and VAC have an inverse mathematical relation

Related by this formula (VAC=Ea/Ees=1/FEVS – 1), the 2 parameters have a divergent curvilinear relation, having a crossing point for the value 1/Φ (0.618). Stepping away from this crossing point to the left or to the right, describes a physiological anomaly because V0 becomes unknown. For the normal interval for LVEF (0.55-0.65), the corresponding normal interval for VAC should be between 0.82 and 0.54. For a wider normal LVEF range (i.e. 05-0.65), including the ambiguous grey zone for LVEF (0.5-0.55), the calculated VAC normality interval becomes 0.54 to 1. Literature data support this interval - the normal VAC value in invasive studies is reported between 1 and 0.36. But using this formula (Ea/Ees=1/FEVS – 1) in these intervals becomes a physiological impossibility, because the VAC value >1 would correspond to an abnormal LVEF value <0.5 - this being the decoupling point.

II.1.Conclusions

As long as we use simplified formulas based on dimensionless ratios and liniar relations, the mathematical rules will expose us to unphysiological result-informations. We have demonstrated that for normal hearts, LVEF and the Ea/Ees ratio would be equal for 0.618 value and V0 will be 0ml - the 2 elastances being in a relationship based on the Phi factor. For this value, the relationship between LVEF and VAC is reduced to the fundamental property of Phi number, and only true for V0=0ml. The Ea/Ees ratio remains a valuable clinical tool, because of the more dynamic variations as compared to those of LVEF, in patients with HF and reduced LVEF and/or unstable critical hemodynamic alterations, but, to the contrary would appear less robust in patients with HF and preserved LVEF.

The fundamental relation between the heart and the periphery as expressed by the VAC remains little used, probably due to the tendency to reduce it to a volumetric ratio and by this, loosing its fundamental meaning. We should persevere to avoid oversimplification and to improve the VAC concept in order to increase its clinical utility.

II.2. Invasive study using right and left heart catheterise for the evaluation for effective arterial elastance formulas in a group of advanced HF patients.

We prospectively included 12 advanced HF patients. The patients had had a recent HF decompensation, but were all evaluated in the condition closest possible to euvolemia, as guided by clinical and echocardiographical criteria. These patients were evaluated by transthoracic echocardiography and in the same day, by right and left catheterise. Ea was calculated using invasive measurements (Ea(i)) using the 2 single-beat available formulas - the original more complex Segers formula and respectively, Kelly's simplified formula. The invasive results for Kelly's Ea formula were afterwards compared to the non-invasively derived measurement (Ea(eco)).

An excellent positive liniar correlation was found, having a high statistical significance, between Ea(i) values obtained by the Kelly formula and those obtained by Segers formula, having a correlation index R=0.9527, p=0.00000171, with a very narrow confidence interval (95%CI [0.8359 , 0.987]), with a small variation coefficient of 0.3797. When comparing Ea(i) Kelly with the echocardiographically derived Ea, a significant positive correlation was found: Ea(i) Kelly - Ea(eco) Kelly approximating ESP as 0.9TAS; *r=0.8047, p=0.01601, 95%CI* [0.2309 , 0.9632]. To the best of our knowledge, this has not been previously described, as there are no specific studies comparing the hemodynamic formulas in this specific patient group. Kelly's formula uses simple and readily accessible parameters and this is why it is commonly used in clinical practice in the critical care setting. Describing this relation is especially relevant to clinical practice, as expanding the use of Ea to the routine evaluation of the HF patient should be currently mandatory.

II.3. Investigating the complex hemodynamics by transthoracic echocardiography in patients with advanced chronic HF

We sought to investigate the hemodynamic status of an advanced chronic HF patient cohort and compare it to an asymptomatic patient group having only minor structural/functional abnormalities, using transthoracic echocardiography. We prospectively included 18 advanced HF patients (HF stage D according to the present HF classification system) and 12 asymptomatic patients (HF stage B).

Echocardiographic parameters for the LV function (including LVEF, LV ejection force), LV dimensions and hemodynamic parameters CPO, VAC maitain their ability to separate advanced HF patients form pre-HF patients, but are dependent to loading conditions and loose their discriminating power to identify the worst prognosis patients.

We have identified an asymmetric distribution of Ea in the advanced HF patient group witch was also demonstrated in the overall patient group, as its values were independent from LVEF and LV ejection force. The correlations were poor when compared to indexed ESV and systolic time index, but we identified a meaningful significant statistical correlation to Ees values ($r=0.766$, $p<0.001$). Ea phenotypes are very diverse for the same narrow LVEF interval, but the Ea variation should not be considered to be chaotic. The strong correlation to Ees values suggests a peripheral hemodynamic 'adjustment'. The complete evaluation of contractile alterations requires the evaluation of Ees dynamics, as LVEF is not informative enough in severely dilated hearts.

II.4. Improving non-invasive formulas for Ees and VAC, in patients with chronic HF with reduced LVEF

Summary: Integrating fundamental parameters such as systolic times, systolic blood pressure, stroke volume together with LVEF can create new, simple to use formulas, very well correlated with Chen's formula for Ees, which have the potential to overcome the disadvantages of LVEF and VAC as dimensionless indices.

For the most severe HF patients, echocardiographic parameters other than LVEF are more robust. On the other hand, we have shown that the peripheral hemodynamic response is very heterogenous even in very similar clinical conditions, while VAC itself being more dynamic than LVEF. We have also demonstrated that VAC, without a known correct value for V0, will be reduced to a dimensionless number, and a simple volumetric ratio, will fail to reflect the real hemodynamic status.

The non-invasive computation of Ees is most likely an approximation, but even so - this approximation is essential to the understanding of the hemodynamics of patients with HF. Nonetheless, the Ees formulas published so far are complex, difficult to use and are therefor poorly assimilated to clinical practice use.

We aimed to test different cardiovascular hemodynamic indices, computed or measured by non-invasive transthoracic echocardiography in order to evaluate their capacity to predict severely

symptomatic HF, beyond LVEF. There parameters included Ees, Ea, VAC, CPO and systolic times. We also tested the relationship between Chen's formula for Ees and simple formulas based on systolic times, pressure and LV volume.

We investigated 33 patients, having a valid thorough transthoracic echocardiographical evaluation (all investigated for clinical routine indication), that we divided in 2 separate groups:

- group A - 12 patients being at risk for HF or Gavin asymptomatic HF (HF stages A and B);
- group B - 21 patients having symptomatic HF (stage C) and advanced HF (stage D), with reduced LVEF; although all patients were analysed at a moment without clinical systemic congestion (being in aparent euvolemia), they had significantly elevated levels for natriuretic peptides;

Among the new indices, we sought to identify the most discriminative between groups A and B, and the ones having the best correlation with Ees and/or VAC.

Chen's Ees formula was weakly positively correlated to LVEF and negatively correlated with indexed ESV (ESVi). The fact that it was much better correlated to pre systolic period (PEP), the ratio PEP/LVET and with the pulse pressure (PP), would suggest the potential of combining pressure, time and volume to create a composite index, comprised of the fundamental elements for Chen's formula.

We developed formulas based on fundamental parameters such as SBP, PEP, VEF, SV - for which we found an excellent correlation with Ees values as calculated using Chen's formulas. We therefore developed a regression model:

*Ees predicted (mm Hg/ml) = 0.225677 * TAS* $^{0.866345}$ ** PEP/LVET* $^{-0.549979}$ ** LVEF* $^{0.325433}$ ** SV* $^{-1.005615}$ *(mm Hg/ml);* ($R = 0.952030$; $R^2 = 0.906360$; R^2 adj. $= 0.892983$; $p < 0.001$).

THe proposed model had the best prediction value for ees, having the advantage of using small indices (and thus avoiding the complexity of using a 7 index for the systolic time ratio as it is necessary for Chen's formula). The ratio PEP/LVET and LVEF were significantly correlated, having an excellent determination coefficient for VAC *(R = 0.9343; R2 = 0.8730; R2 adj. = 0.8645; p< 0.001);* the following logarithmic regression equation resulted: *VAC predicted = 7.057490 * PEP/LVET* $^{0.552265}$ ** LVEF* $^{-0.297602}$. Basically, this equation is dimensionless.

Conclusions and personal contributions

The research of this dissertation describes several new ideas/concepts, unpublished before.

In the firs study, we demonstrated that for the normal hearts, LVEF and VACwill be equal only for the value of 0.618, and in this situation V0 can only be 0ml.

For the pathological situation, when LVEF slides further from this value, the LVEF-VAC relationship is no longer liniar, and calculating VAC through the simplified volumetric formula will lead to the loss of fundamental meaning and to unreasonable values. We further fundamental this mathematical reasoning in the last study, by showing that the values obtained by the simplified VAC do not have the normal, expected distribution. Calculating Ees and VAC through simplified formulas should not be used in clinical practice.

In the patient groups having symptomatic HF with reduced LVEF, we aimed to investigate if the simplified formula for the Ea developed by Sunagawa and Kelly would have comparable results to the more elaborate formula developed by Segers. In the second study, we demonstrated that Ea values obtained by the simplified formulas are comparable and have an excellent positive correlation with the Ea values of the more elaborate formula. We therefor concluded that calculating Ea using the simplified formula ESP/SV is readily available and robust enough for routine clinical practice. We also obtained significant correlations between the invasive fundamental measurements and the echocardiographic ones, except for the CPO. CPO is a very robust marker, but only validated for invasive studies. Echocardiographic measurement seems to be more relevant for the formula proposed by Chemla. This study was also an internal validation study for the relevance and utility of hemodynamic research using echocardiography.

In the third study, we identified an important hemodynamic heterogeneity in patients with advanced HF, when compared with a group of asymptomatic patients - as represented by an important variation of Ea values. This observation has been previously described in just one recent analysis. This meta-analysis identified Ees as the fundamental parameter that defines the evolution of HF patients throughout the different A to D stages. When integrating this observation with the one in our study in which the peripheral hemodynamic response (as measured by Ea) was

independent from classical parameters (i. LVEF, ESV) but positetely correlated with Es (as calculated by Chen's formula), we consider that VA interaction is paramount for the HF patients.

In the final part of the research we investigated whether the extremely elaborated formula for Ees, developed by Chen, could be replaced by simplified formulas.

We consider that incorporating fundamental parameters, with a relevant physiological meaning and easy to measure such as SBP, PEP, SV could be a solution to improve the clinical relevance of dimensionless indices such as LVEF, VAC> We therefor identified several formulas using such parameters, that were excellently correlated with Chen's formula for Ees and than to VAC. We have shown that the simple ratio between SBP and PEP can be very informative for patients with symptomatic HF; it was significantly correlated to Chen's formula for Ees and could discriminate the severe patients. The regression models we proposed based on these formulas would predict Chen's Ees and VAC's calculated values with a significant accuracy - having a risk of error of below 5%. These simple measurements would answer to the problem of incorporating too complex formulas, with a high risk of error into clinical practice.

We consider that translating into clinical practice the calculation of Ea, Ees and VAC is necessary and presently accessible. Cardiologists should persevere to avoid oversimplification and improving the VAC concept to increase its clinical value.

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