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Effective Arterial Elastance and Arterial Compliance in Heart Failure Patients with Preserved Ejection Fraction

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Abstract— **Heart failure (HF) patients have often been observed to have their ejection fractions somewhat preserved (HFpEF). Since left ventricular (LV) ejection is dependent on the coupled arterial load, the preserved ejection may be dependent on the effective arterial elastance (Ea). Whether this is indeed the case is subject to further analysis. We investigated this aspect in 67 patients with cardiac disease; 34 of them met the matching criteria for HFpEF. Both Ea, an arterial system (ASy) property, and aortic compliance (C), a physical property, were obtained in an attempt to differentiate the LV-ASy interaction in HFpEF and HFrEF (reduced ejection fraction) patients. Outcome of the study allowed us to conclude that Ea does not parallel changes in C. While Ea may be useful in assessing the severity of HFrEF, it is a weak indicator of EF dependence in HFpEF patients.**

I. Introduction

The heart is naturally coupled to the arterial system, and as such, its ejection is dependent on the properties of the aorta and the distributing arteries. Thus the interaction of the heart and the arterial system is utterly important in governing proper function of the cardiovascular system [1]. Left ventricle-arterial system (LV-ASy) interaction has been described in terms that include maximal elastance (Emax) of the LV and effective arterial elastance (Ea) of the arterial system. Their ratio Emax/Ea describes how LV and ASy interact [2,3]. This underlies the belief that Emax can be used as index of cardiac contractility and that Ea can sufficiently account for arterial system hemodynamic properties.

Mismatch regarding hemodyamic coupling (k) between LV and ASy has been reported both in human patients and in dogs with heart failure (HF) [3,4]. It has been found that coupling is no longer optimal in heart failure patients. More recent clinical studies have shown there is a subset of heart failure patients who have preserved ejection fraction (HFpEF) close to normal. This seemingly suggests that their arterial system properties may be also preserved. These patients differ from those heart failure patients with reduced ejection fraction (HFrEF).

The arterial system, in terms of its dynamic pressure-flow relations, can be described by the characteristic impedance of the proximal aorta (Zo), the total arterial compliance (C), and the peripheral vascular resistance (PVR) [1,5]. The aortic compliance is of utter importance during ejection, thus its alteration can significantly modify LV ejection. It is a physical property directly dependent on the elastic behavior of the aorta.

We hypothesize that incorporating effective arterial elastance (Ea) and aortic compliance can allow differentiation of HFpEF patients from HFrEF patients in terms of how well their left ventricles interact with their respective arterial systems and that the physical properties of the arterial system may provide a better identification of the differences. To test this hypothesis, we performed analysis employing clinical patient data.

II. Methods

A. Patient Data

Patient data were obtained retrospectively. All patients had LV end-diastolic pressure (EDP) > 16 mmHg, which is a characteristic of HF. Only those (n=67) without beta-adrenergic blockers were included in the study, because these agents have been demonstrated to alter LV volume regulation [6,7,8]. Angiography was used to determine end-systolic volume (ESV) and end-diastolic volume (EDV) in patients with pEF (n=34) and a control group with rEF (n=33). Volumetric data are normalized for body surface area, i.e. mL / m^2. Pressures were recorded through the pigtail catheter used for the LV angiogram. After de-bubbling, the catheter was connected through short stiff tubing to a Statham P23Db strain gauge manometer, previously calibrated against an external mercury manometer. Timing of the LVEDP corresponds to the R-wave intersection with the LV pressure tracing. End-systolic pressure (ESP) was estimated as 0.9 * LV systolic pressure. LV maximum systolic elastance (Emax) was calculated as:

$$Emax = ESP / (ESV-Vo) \quad (1)$$

where the intercept Vo is assumed to equal zero. Effective arterial elastance (Ea) was assessed as

$$Ea = (ESP) / (EDV-ESV) \quad (2)$$

and ejection fraction

$$EF = (1-ESV / EDV)\ 100\% \quad (3)$$

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is expressed as percentage. Hemodynamic coupling (k) between left ventricle and arterial circulation is defined as

$$k = Emax / Ea \quad (4)$$

which is the ratio of two elastances, and therefore represents a dimensionless number.

Arterial compliance (C), a parameter describing the physical property of the arterial system, is calculated as the ratio of stroke volume (SV) to pulse pressure (PP) [1,5,9]:

$$C = SV / PP \quad (5)$$

where SV is the difference between EDV and ESV, while PP is defined as the difference between systolic and diastolic arterial pressure.

Finally, peripheral vascular resistance (PVR) is given by

$$PVR = MAP / CO \quad (6)$$

where MAP is mean arterial pressure, while CO is cardiac output (i.e. the product of heart rate and SV).

B. Statistical Analysis

Linear regression analysis and Fisher z-transformation were applied.

III. RESULTS

Calculations of the ventricular and arterial elastances show that in heart failure patients with reduced ejection fraction (HFrEF) the EF is almost linearly proportional to the ratio of Emax / Ea with a steep slope. However, heart failure patients with preserved ejection fraction (HFpEF), show a much smaller slope when EF is plotted against Emax/Ea. (Fig. 1).

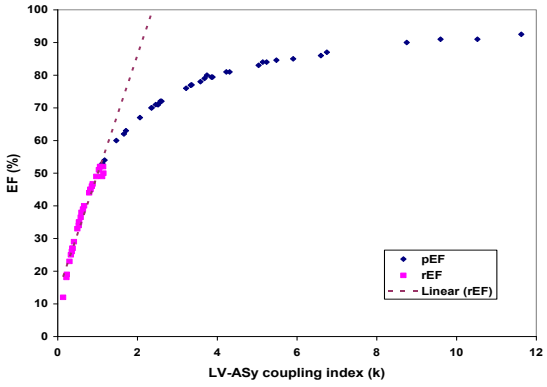

Fig. 1. Ejection fraction (EF) plotted as a function of the ventriculo-arterial coupling index (k). Linearized regression line for rEF group: EF (%) = 36.38 k + 13.34 with $r^2 = 0.9535$ for n=33. The relationship for pEF is clearly nonlinear, while the linearized upper portion generates a slope (not shown) which is less steep.

The above observations can be dissected through the composition of the ventricular and arterial system properties. Figure 2 shows that peripheral vascular resistance PVR (see Eqn. (6), when plotted against arterial compliance (C), a physical property, results in a curvilinear and inverse relation. Additionally, it is seen that there is little difference in the curvilinear relations that separate the HFpEF group from the HFrEF group.

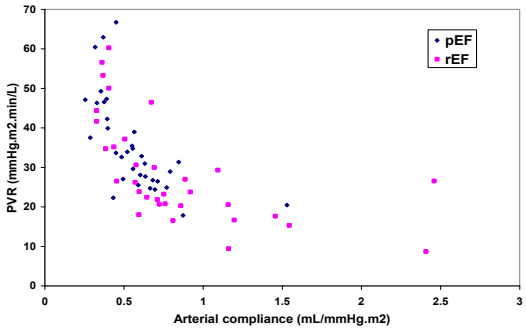

Fig. 2. Scatter plot of peripheral vascular resistance (PVR) against arterial compliance (C) for both the preserved ejection fraction (pEF) and reduced ejection fraction (rEF) heart failure patient groups.

When ejection fraction is plotted against PVR for both groups, as shown in Figure 3, it is evident that persistently "normal" ejection faction is seen among HFpEF patients, despite several folds of changes in peripheral resistance:

$$pEF = -0.2379\ PVR + 84.958 \text{ with } r^2 = 0.0782, n=34 \quad (7)$$

In contrast, more drastic changes in ejection fraction are seen in the HFrEF patients when peripheral resistance increases:

$$rEF = -0.5036\ PVR + 55.929 \text{ with } r^2 = 0.1807, n=33 \quad (8)$$

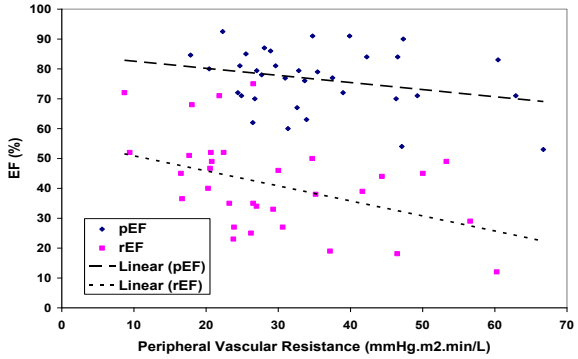

Fig. 3. Ejection fraction (EF) plotted against peripheral vascular resistance (PVR) for both the HFpEF and HFrEF groups of patients.

Ejection fraction when plotted against arterial compliance for both preserved and reduced ejection fraction groups, yields a striking difference in the dependence of EF vs. C:

$$pEF = 1.7263\ C + 75.55,\ r=0.04\ (ns),\ n=34 \qquad (9)$$

$$rEF = 13.16\ C + 30.13,\ r=0.412\ (p<0.05),\ n=33 \qquad (10)$$

That is: EF rises with increasing C in HFrEF patients. However, in HFpEF patients, there is practically no observed dependence of EF on C (i.e. r is not statistically significant).

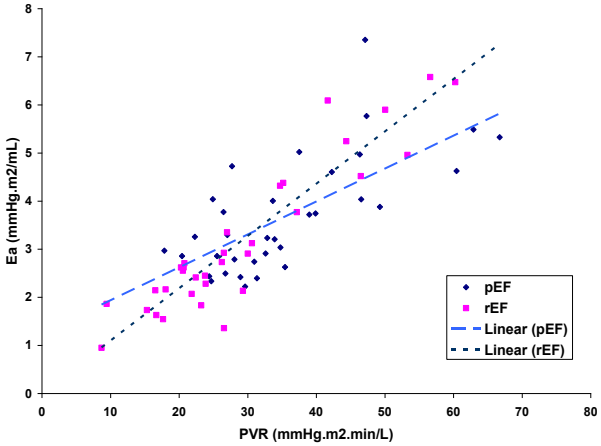

Fig. 4. Effective arterial elastance (Ea) versus PVR for both HFpEF and HFrEF groups of patients.

For comparison, we also show a graph (Fig. 4) of Ea versus PVR for both patient groups, along with their regression equations:

$$\text{for pEF: } Ea = 0.0684\ PVR + 1.2544,\ r^2 = 0.4755 \qquad (11)$$

$$\text{for rEF: } Ea = 0.1087\ PVR + 0.0123,\ r^2 = 0.8807 \qquad (12)$$

That is: Ea is primarily and significantly dependent on the peripheral resistance or PVR.

Finally, Fig. 5 illustrates how EF relates to Ea. Linear regression analysis yields the following equations with slightly better correlation for the HFrEF case:

$$pEF = -2.5534\ Ea + 85.922,\ r^2 = 0.0887\ (n.s.) \qquad (13)$$

$$rEF = -4.1003\ Ea + 54.305,\ r^2 = 0.1645\ (p<0.04) \qquad (14)$$

The immediate visual conclusion drawn from Fig. 5 is not surprising, as the regression lines are quite similar to those in Fig. 3. This is because Ea, a system property, is primarily determined by PVR as demonstrated in Fig. 4.

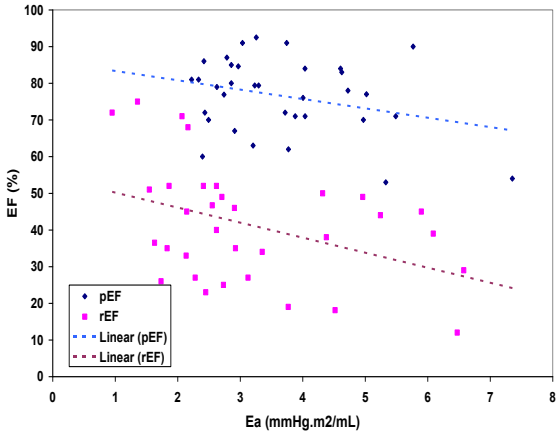

Fig. 5. Ejection fraction (EF) versus effective arterial elastance (Ea) for both HFpEF and HFrEF. Symbols the same as in Fig. 4.

IV. DISCUSSION

Clinical data have shown that almost half of all patients with heart failure (HF) are diagnosed as having a preserved ejection fraction (pEF) with EF > 50% and EDV < 97 mL/m^2 [4]. This puzzling observation indicates that ejection fraction alone is not a good index of the performance of the heart.

Studies of heart-arterial system interaction showed time-varying elastance properties for both the left ventricle (LV) and the ASy [10]. A simplified ratio of maximum elastance of the left ventricle (Emax), to that of the effective arterial elastance, Ea, can be used to describe the coupling between the LV and ASy [2]. However, Ea is predominantly determined by peripheral vascular resistance (PVR), see Fig. 4. Thus, Ea (as a measure of the functional properties of the arterial system) does not parallel changes in arterial compliance (C), a physical property. It is shown here that while Ea may be useful in assessing the severity of heart failure patients with reduced ejection fraction (Fig. 3), it is a weak indicator of EF dependence in HFpEF patients (Fig. 5).

The surprising evaluation outcome is demonstrated where for arterial compliance a clear differentiation between the HFpEF group and HFrEF group is demonstrated (cf. eqns 9 and 10). It is obvious that heart failure patients with preserved ejection fraction display an ejection fraction that is practically independent of changes in arterial compliance. In the heart failure patients with reduced ejection fraction, EF tends to rise with an increase in arterial compliance. Thus, in this HFrEF group of patients, therapeutic drugs that improve arterial compliance can significantly improve overall LV-ASy coupling and hence overall cardiac performance.

We limited our analysis to patients not using betablocking medications, in order to eliminate interference with intrinsic LV volume regulation [6,7,8]. However, future studies should scrutinize on these possible influences, including anticipated effects of comorbidities such as diabetes mellitus.

Modeling studies have been shown [7, 11] to predict e.g., optimal hemodynamic coupling properties in terms of maximizing stroke work. In clinical practice, it is not easy to estimate the coupling index k (Eqn. 4) because determination of the intercept Vo (Eqn. 1) is rather complex in the clinical setting. Therefore, in clinical studies the value of Vo has often been neglected [12], as we have also done in the present study. Future consideration of recent investigational outcomes of determining Vo from e.g., transient vena cava occlusion as performed in experimental dogs [4], and the application of selected pharmacologic interventions or measurements obtained during exercise in heart failure patients [13] will certainly enhance our understanding of LV-ASy interaction in both groups of patients.

More detailed analysis of arterial properties (e.g., in terms of input impedance and viscoelasticity) can be performed by measuring aortic pressure, diameter, and flow waveforms [1,5] as was previously experimentally demonstrated in studies involving sheep [14], horses [15] and dogs [16].

Furthermore, we assumed that ESP can be estimated as 0.9 * LV systolic pressure, in line with comparable studies [12].

LV filling pressure is elevated in HF patients, indicating diastolic dysfunction. Therefore, estimation of Ea (Eqn. 2) was refined by taking into account the actual level of EDP, which is known to be considerable in heart failure patients, namely often substantially above 16 mmHg [4]. EDP reflects the level of right atrial pressure.

Better insight in LV-ASy interaction will also contribute to the refinement of artificial afterload systems, such as the *Hofkessel* [17], which can control arterial system properties on the basis of any selected value for either mean pressure, mean flow (cf. CO) or vascular resistance (PVR).

The theoretical relationship between EF and k can easily be derived when Vo is assumed to vanish (as was done in the present study and also elsewhere e.g., [12]). Then it can be derived that EF = 1 - 1 / (k+1) [18]. This equation largely explains the general findings illustrated in Figure 1.

Future studies may concentrate on HFpEF and HFrEF patients with significant aortic stenosis, and thus complement earlier model-based studies in this area [19].

V. CONCLUSION

The combined use of peripheral vascular resistance (PVR) and arterial compliance (C) may be more superior to using effective arterial elastance (Ea) alone in differentiating HFpEF versus HFrEF patients. Heart failure patients with preserved ejection fraction seem to be decoupled from the arterial system, in that their ejection fractions are relatively independent of changes in resistance or compliance.

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