Author’s response to reviews

Title: Area of the pressure-strain loop during ejection as non-invasive index of left ventricular performance: a population study

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Response to Reviewers

Reviewer #1: I admire the authors' effort. The problem of precise evaluation of the impact of afterload on the heart function has an incremental clinical value. The way the paper is written is not clear for me in the methodology section.

• Comment 1: It is not clear even in the supplementary material: "The software was validated in 50 subjects using intermediate and final quality checkpoints and is available upon request from the corresponding author". Does it mean that there was no validation on the invasively checked pressure loops or invasive blood pressure measurements? It was only checked by the use of software on the already obtained data?

Taking into account the epidemiological settings of our study we did not perform the invasive validation of pressure-strain loops or measure invasive blood pressure in our general population cohort (not patients). However, previous invasive experimental and clinical studies have already validated the proof of concept of pressure-strain loop construction (for reference see Urheim S,
Am J Physiol Heart Circ Physiol. 2005;288(5):H2375-80 and Hubert A, Eur Heart J Cardiovasc Imaging. 2018;19(12):1372–9. Moreover, the finger tonometric device has been also validated previously against intravascular blood pressure measurements in patients (e.g. Eckert S, Blood Pressure Monitoring 2002).

On the other hand, in our study, we did need to check the software’s performance as this is a custom made software written for constructing pressure-strain loops and calculating EWD from simultaneously recorded non-invasive finger tonometric and echocardiographic data. As requested by the Reviewer, we clarify in the Methods that: “The performance of the software was validated in 50 subjects using …” (page 5, final paragraph).

- Comment 2: It is not clear for me why only 54.4% patients with hypertension was treated (do you have access to the medical records of those patients, how was defined the definition of hypertension)

Please, note that the FLEMENGHO study includes subjects that have been randomly recruited from the general population, i.e. not via hypertensive clinic. The participants classified as having untreated hypertension include mainly subjects who were unaware that they had high blood pressure. They might have never been screened for hypertension before or they might do not have high blood pressure during previous screenings. Our data are in line with previously reported screening results in general population. For instance, among 13,947 US adults aged ≥18 years enrolled in the Third National Health and Nutrition Examination Survey, 52.5% were also untreated (Zhou D, Scientific Reports, 8: 9418).

We defined hypertension based on conventional blood pressure measurements performed at the examination center and/or use antihypertensive medication. As suggested by the Reviewer, we moved the definition of hypertension from the Data Supplement to the main manuscript: “Conventional blood pressure was the average of 5 auscultatory readings obtained with the subject in seated position. Hypertension was defined as a conventional blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic and/or the use of antihypertensive drugs.” (page 6, second paragraph).

- Comment 3: Furthermore, adjusted EWD was significantly greater in both treated and untreated subjects with hypertension as compared to normotensive subjects. Could you explain it in discussion section - it is not clear for me.

As suggested by the Reviewer, in the revised manuscript we further explored the differences in EWD between treated and untreated participants with hypertension (HT) by subdividing the treated group according to controlled or uncontrolled blood pressure. Of note, unadjusted and
adjusted EWD were significantly higher in both untreated HT (767.6 Pa; P=0.018) and uncontrolled HT (795.5 Pa; P=0.0036) as compared to controlled HT (690.2 Pa). In addition, EWD did not significantly differ between normotensive subjects and those with controlled hypertension (P=0.49). As such, our findings suggest that hypertension elevates EWD, but that antihypertensive treatment might lower EWD if blood pressure is controlled successfully.

In the revised manuscript we first added the definition of controlled and uncontrolled HT to the Method Section (page 6, second paragraph). Second we updated Figure 3A with information on EWD in the controlled and uncontrolled HT groups (page 26). Third, we described these results in text: “Furthermore, adjusted EWD was significantly greater in participants whose hypertension was either untreated (P=0.018) or uncontrolled (P=0.0036) as compared to subjects with controlled hypertension (Figure 3A). Of note, EWD did not differ between normotensives and subjects with controlled hypertension (P=0.49; Figure 3A)” (page 7, final paragraph). Forth, we added to the Discussion section the following sentences: “we confirmed that hypertensive subjects had a higher pressure-strain area than normotensive participants if untreated or if their hypertension was uncontrolled, … . In contrast, EWD was not different between normotensives and effectively controlled hypertensives. Evidently, the observational and cross-sectional nature of our study did not allow to infer causality between controlled hypertension and normalization of EWD.” (page 11, first paragraph).

• Comment 4: In my opinion you should performed detailed analysis for the correlation with antihypertensive drugs, ACE-I have different influence than diuretics, especially aldosterone antagonists

As requested by the Reviewer, we investigated the relationship between EWD and the different classes of antihypertensive treatment. In multivariable-adjusted analysis, EWD decreased with the use of β-blockers (-65.4±31.4 Pa; P=0.046). In contrast, EWD was not related to the use of ACE-inhibitors/ARBs, calcium channel blockers or diuretics after full adjustment (P≥0.51). We described these findings in the Results section (see page 8, second paragraph).

Please, note that the cross-sectional and observational nature of our population study does not allow us to infer causality between β-blocker therapy and lowering in EWD. Likewise, absence of a cross-sectional relationship between EWD and the other classes of antihypertensive drugs does not necessarily disprove effects of these drugs on EWD.

• Comment 5: The crucial thing in my opinion is the correlation of stiffness of the myocardium and the arteries. According to the new diastolic guidelines I have not seen the values of TRPG.
Clinically relevant tricuspid regurgitation as defined by the new diastolic recommendations is not often seen in the general population. For instance, only 12 of 1000 participants (1.2%) of the EPIPorto study presented with a TR peak velocity >2.8 m/s (Almeida, Eur Heart J Cardiovasc Imaging 2017). In line, of 1407 FLEMENGO subjects, only 13 subjects (0.92%) exceeded the TRPG threshold of 2.8 m/s (paper under review). A TR velocity of more than 2.8 m/s might rather indicate clinically relevant pulmonary hypertension in advanced stages of heart failure (Lam, J Am Coll Cardiol 2009) than be an indicator of early diastolic dysfunction in asymptomatic subjects at high cardiovascular risk (for instance ambulatory hypertensive subjects).

Comment 6: Interesting may be a comparison of those parameters like EWD in patients according to the diastolic function (with regard to the guidelines of EACVI). Especially LAVi was three times bigger in women (in Parameter estimates)

We agree with the Reviewer that it would be interesting to make a comparison between participants with normal and abnormal LV diastolic function. Unfortunately, the updated recommendations on assessment of diastolic function were mainly designed to evaluate LV filling pressure in symptomatic heart failure patients (advanced stages). Recent population studies have legitimately questioned the applicability of this algorithm in detection of early LV diastolic dysfunction pattern in asymptomatic patients at high cardiovascular risk (e.g. with hypertension, diabetes, etc.). Indeed, application of these recommendations to a general population results in a low number of subjects fulfilling the criteria for having LV diastolic dysfunction. For instance, in 1000 EPIPorto subjects (≥45 years) recruited from the general population, the prevalence of LV diastolic dysfunction dropped from 38.1% to 1.4% when shifting from the 2009 to the 2016 ASE/EACVI criteria (Almeida, Eur Heart J Cardiovasc Imaging 2017). Similarly, only 20 of 1485 STANISLAS participants (1.3%) had diastolic dysfunction according to the 2016 ASE/EACVI criteria, whereas prevalence of diastolic dysfunction ranged from 5.7% to 8.8% when using previous expert recommendations (Huttin, J Am Coll Cardiol 2017). In our community-based FLEMENGO sample including 1407 subjects between 18 and 90 years old, prevalence of diastolic dysfunction dropped also to 1.9% when applying the 2016 ASE/EACVI approach as compared to 16.7% when we applied previously used FLEMENGO criteria (paper under review). As acknowledged by writers of the guidelines (Edvardsen T, Eur Heart J Cardiovasc Imaging 2018), the new algorithm results in higher specificity at the cost of lower sensitivity to diagnose diastolic dysfunction particularly in those with early asymptomatic stage. When applying the recommendations to our current sample of 356 community-dwelling participants, only a handful of participants are labelled as having LV diastolic dysfunction. Evidently, this is too few to do a proper statistical comparison. However, we performed the requested analysis by using our population based diastolic dysfunction criteria. Unadjusted EWD was significantly higher in subjects with LV diastolic dysfunction (n=30) as compared to the rest of the cohort (823 Pa vs 686 Pa, P=0.013).
Comment 7: "EWD decreased independently with LV wall thickness in men, yet increased with higher LAVi and LV filling pressure (E/e' ratio) in women only" - could you explain why? The increased thickness and LV filling pressure should increase the stiffness and fibrosis of the myocardium. Why there are opposite sex results? Influence of treatment, concomitant disease?

We use EWD as a surrogate marker for LV performance (work) which depends on LV wall stress. In turn, LV wall stress decreases with LV wall thickening and increases with higher LV pressure and internal diameter according to the law of Laplace. In our study, we observed that EWD decreased with LV wall thickening, but only in men. This finding suggests that LV concentric remodeling might lower LV wall stress in men (e.g. to compensate for increased afterload), but that this compensatory mechanism might fail to normalize LV wall stress in women. On the other hand, EWD increased with echocardiographic indexes reflecting diastolic dysfunction (e.g. high LA volume, high E/e') in women but not in men. The latter might suggest that LV diastolic dysfunction increases LV wall stress (EWD) predominantly in women, or that, in reverse, the LV diastolic function of women is more sensitive to increased LV wall stress. We proposed in Discussion that this sex-dependent relation between LV wall stress and LV geometry and function might be explained by the on average smaller hearts, higher systolic performance and higher diastolic elastance of women as compared to men. Evidently, the observational nature of our study did not allow to assess whether differences in treatment or concomitant disease might explain the differences between sexes.

Comment 8: Could you explain why there is such big difference in adjusted EWD (Pa).

We would kindly ask the Reviewer to specify which difference in adjusted EWD is big. The substantial difference in EWD (both unadjusted and adjusted) between age tertiles and between normotensive/hypertensive subjects are particularly mediated by a steeper and stronger rise in pulse pressure (typically associated with aging and hypertension). In women, pulse pressure rises steeper and stronger with age as well, plus their systolic strain reaches higher levels as compared to men. This is illustrated in the average pressure-strain loops in Figure 2B-C and Figure 3A.

Reviewer #2: In the paper entitled "Area of the pressure-strain loop during ejection as non-invasive index of left ventricular performance: a population study" the authors investigated the anthropometric and clinical determinants of ejection work density (EDW) and also explored the relationship of EWD with indexes reflecting LV structure, LV diastolic function and arterial stiffness in a fair number of patients derived from the FLEMENGO study. It is important that the authors performed pressure waveforms analysis instead of taking the systolic pressure as adopted in the myocardial work analysis. Some issues need to be clarified:

Comment 1: Which were the baseline illnesses?
Our epidemiological study includes subjects that were randomly recruited from the general population for a technical examination at our study center. During the examination, we obtained the participants’ medical history and determined several cardiovascular risk factors (e.g. blood pressure levels for definition of hypertension, fasting glucose levels for definition of diabetes mellitus, etc.). All self-reported diseases were ascertained against medical reports obtained from the participant’s general practitioners and from hospitals located around the examination site. All subjects were visiting our examination center and did not have any severe stage of disease required hospitalization. Among others, we observed following diseases in our population sample at the time of examination: hypertension (n=169, 47.7%), diabetes mellitus (n=16, 4.5%) and coronary heart disease (n=7, 2.0%).

Comment 2: Treated HT does not define the subgroup well enough: Is the hypertension controlled or not. This raise curiosity because EDW values overlaps completely between the adjusted treated and untreated groups.

As requested by the Reviewer, we subdivided the participants treated for hypertension (HT) into a controlled (n=44) and an uncontrolled group (n=48). We defined controlled HT as being on antihypertensive treatment with a blood pressure below 140 mmHg systolic and/or 90 mmHg diastolic. Of note, adjusted EWD was significantly higher in both the untreated (767.6 Pa; P=0.018) and the uncontrolled HT groups (795.5 Pa; P=0.0036) as compared to the controlled HT group (690.2 Pa). In addition, EWD did not significantly differ between subjects with normotension and those with controlled hypertension after full adjustment (P=0.49).

In the revised manuscript we first added the definition of controlled and uncontrolled HT to the Method Section (page 6, second paragraph). Second we updated Figure 3A with information on EWD in the controlled and uncontrolled HT groups (page 26). Third, we described these results in text: “Furthermore, adjusted EWD was significantly greater in participants whose hypertension was either untreated (P=0.018) or uncontrolled (P=0.0036) as compared to subjects with controlled hypertension (Figure 3A). Of note, EWD did not differ between normotensives and subjects with controlled hypertension (P=0.49; Figure 3A)” (page 7, final paragraph). Forth, we added to the Discussion section the following sentences: “we confirmed that hypertensive subjects had a higher pressure-strain area than normotensive participants if untreated or if their hypertension was uncontrolled, … . In contrast, EWD was not different between normotensives and effectively controlled hypertensives. Evidently, the observational and cross-sectional nature of our study did not allow to infer causality between controlled hypertension and normalization of EWD.” (page 11, first paragraph).

Comment 3: The authors assessed multivariable-adjusted associations of EWD with anthropometric and clinical characteristics, hemodynamics, arterial stiffness and
echocardiographic indexes of LA volume index (LAVi) and LV structure and function by using mixed models. All models were adjusted for age, sex, heart rate and body height and weight, and accounted for family clusters modelled as a random effect. However the corresponding table are not self-explanatory and may be confusing for the reader.

As requested by the Reviewer, we adapted the legends of Tables 3- 5 to make them more self-explanatory (pages 21-23).

• Comment 4: I would expect an influence of heart rate which is also higher in women, as reader for example.

In our study, EWD did no correlate with heart rate in univariate linear regression (correlation coefficient \( r=-0.024, \ P=0.67 \)) nor in multiple linear regression analysis adjusted for important confounders such as age, sex and hypertension (effect size on EWD per 15 beats per minute increase in HR=-18.9 Pa; \( P=0.23 \)). As requested by the Reviewer, we added to the text that: “In both unadjusted and fully adjusted analysis, EWD was not associated with heart rate (\( P\geq0.23 \)).” (page 8, second paragraph).

As mentioned in text (page 7, final paragraph), the sex-specific EWDs presented in Figure 2 were adjusted for heart rate and thus for the observed difference in heart rate between men and women. For completeness, we added the list of variables for which we adjusted to the heading of Figure 2 and 3 (pages 25-26). As mentioned in the manuscript’s text and table legends, all multivariable-adjusted associations between EWD and blood pressure/echocardiographic components were accounted for heart rate.

• Comment 5: There might be a confounding effect of ACE/ARB use as well as smoking. Are the authors concerned about this?

In the revised manuscript, we acknowledge a potential confounding effect of the different classes of antihypertensive treatment and smoking on EWD.

a) Class of antihypertensive treatment: In multivariable-adjusted analysis, EWD decreased with the use of \( \beta \)-blockers \((-65.4\pm31.4; \ Pa; \ P=0.046)\). In contrast, EWD was not related to the use of ACE-inhibitors/ARBs, calcium channel blockers or diuretics after full adjustment \((P\geq0.51)\). As requested by the Reviewer, we described these findings in the Results section (page 8, second paragraph). Of note, the cross-sectional and observational nature of our study does not allow us to infer causality between \( \beta \)-blocker therapy and lowering in EWD.

b) Smoking: We did not observe a relationship between EWD and smoking. First of all, EWD was not significantly different between the smokers and non-smokers in both unadjusted
analysis (671.6±216.1 Pa vs 707.5±212.9 Pa; P=0.22) or after adjustment for important covariates such as age, sex and hypertension (708.8 Pa vs 709.2 Pa, P=0.99). In support, smoking was not selected as a significant determinant of EWD in stepwise regression (in contrast to age, sex, bmi, and hypertension). As requested by the Reviewer, we mention in the text that: “In both unadjusted and fully adjusted analysis, EWD was not associated with … , nor with smoking (P≥0.22).” (page 8, second paragraph).

- Comment 6: Is it possible to think that one should be cautious when using EWD in women but more confident in men because of associations of ejection work density with echocardiographic indices of left atrial and left ventricular geometry?

This is possible, but further investigation is needed to confirm this statement.