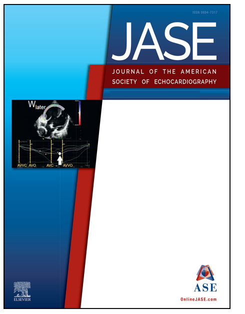
Kleinnibbelink, G, Hulshof, HG, van Dijk, APJ, Cate, TT, George, KP, Oxborough, D and Thijssen, DHJ

Effects of preload manipulation on right ventricular contractility: invasive pressure-area loop versus non-invasive strain-area loop.



Effects of preload manipulation on right ventricular contractility: invasive pressure-area loop versus non-invasive strain-area loop

Geert Kleinnibbelink, Hugo G. Hulshof, Arie P.J. van Dijk, Tim ten Cate, Keith P. George, David L. Oxborough, Dick H.J. Thijssen

PII: S0894-7317(20)30801-4

DOI: https://doi.org/10.1016/j.echo.2020.12.007

Reference: YMJE 4650

To appear in: *Journal of the American Society of Echocardiography*

Received Date: 29 October 2020

Revised Date: 9 December 2020

Accepted Date: 9 December 2020

Effects of preload manipulation on right ventricular contractility: invasive pressure-area loop versus non-invasive strain-area loop

Brief title: RV function after preload manipulation

GEERT KLEINNIBBELINK[a,b](G.Kleinnibbelink@radboudumc.nl)*
HUGO G. HULSHOF[a] (Hugo.Hulshof@gmail.com)*
ARIE P.J. VAN DIJK[a] (Arie.vanDijk@radboudumc.nl)
TIM TEN CATE[a] (Tim.tenCate@radboudumc.nl)
KEITH P. GEORGE[b] (K.George@ljmu.ac.uk)
DAVID L. OXBOROUGH[b] (D.L.Oxborough@ljmu.ac.uk)
DICK H.J. THIJSSEN[a,b] (Dick.Thijssen@radboudumc.nl)

*both authors contributed equally

[a] Research Institute for Health Sciences, Departments of Physiology and Cardiology, Radboud University Medical Center, Nijmegen, The Netherlands
[b] Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, United Kingdom

WORD COUNT: 850
FIGURES: 1

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Disclosures: The authors have no relationships or conflicts to disclose

Author for correspondence: Prof. Dick H.J. Thijssen, Department of Physiology Radboud University Medical Center, Philips van Leydenlaan 15, 6525 EX, Nijmegen, The Netherlands, Email: dick.thijssen@radboudumc.nl, Tel: (+31)24 36 14222, Fax: (+31)24 366 8340

Invasive right ventricular (RV) pressure-volume loop provides the gold-standard to evaluate cardiac contractility, but also provides insight into cardiac function as increases in preload cause a rightward shift of the loop and elevates stroke volume (and *vice versa*). Echocardiography has relevance in evaluating cardiac function but also in mechanics, specifically regarding the dynamic relationship between RV longitudinal strain and RV area; strain-area loop.[1] RV strain-area loop characteristics relate to afterload, whilst characteristics hold independent predictive capacity for morbidity/mortality in pulmonary arterial hypertension.[2, 3] Changes in preload alter cardiac dynamics that may induce shifts in the non-invasive RV strain-area loop (similar to shifts in RV pressure-area loops). To better understand the potential of RV strain-area loops in assessing RV function, we compared the impact of preload manipulation on RV strain-area loop *versus* pressure-area loop, and subsequently compared invasive and non-invasive assessment of cardiac contractility.

We recruited 7 individuals (age 54±14 year, 71% female) undergoing right heart catheterisation (to diagnose pulmonary arterial hypertension). Participants provided informed consent prior to procedures. Study procedures were approved by local ethics committee (Radboudumc). During catheterisation a 24-mm AMPLATZER™ Sizing Balloon II (AGA Medical Corporation, Plymouth, USA) was introduced into the inferior vena cava for manipulation in preload. For direct time-point comparison between pressure, strain and area, we simultaneously recorded invasive RV pressure and 2D-echocardiographic images: 1) at baseline, 2) after intravenous infusion of 500ml saline (to increase preload), and 3) after intra-balloon inflation (to reduce preload). Echocardiographic data were analysed using QLAB V10.8 (Philips, Andover, USA) to measure RVLS and area (as previously described)[3, 4], whilst RV pressure data were retrieved from Mac-Lab (GE Medical, Horton, Norway). After preload manipulation data were recorded within 1-minute after stabilization of the signal.

Mean strain-area loops and characteristics across the time-points were compared using one-way ANOVA.

The increase in preload caused a rightward shift of the pressure-area loop, whilst a decrease in preload caused a leftward shift and reduced stroke volume. These characteristic shifts were also present in the strain-area loop, with an increase in preload inducing RV longitudinal strain decline and a decrease in preload causing an increase in peak RV longitudinal strain. The slope of the systolic phase of the strain-area loop (i.e. Sslope) during preload elevation was significantly smaller than during preload reduction ($-1.8\pm0.7\%/cm^2$ *vs*. $-2.9\pm0.9\%/cm^2$, $P<0.05$). A potential explanation of this finding is that as preload and stroke volume decreases there is a larger contribution of longitudinal fiber shortening with possible less dependency on circumferential fiber shortening to facilitate systolic volume ejection. This also may explain the paradoxical increase in peak longitudinal strain upon preload reduction as circumferential strain may be disproportionally decreased. Since we were not able to measure circumferential strain, this remains speculative. It is important to acknowledge the complexity of RV function, with changes in stroke volume potentially impacting upon various aspects of cardiac mechanics. This makes it difficult in our study to identify a single or most important factor explaining our observations.

Cardiac contractility is presented as the relation between end-systolic area (or volume) *versus* pressure. Using the non-invasive RV strain-area loop, we explored the ability to assess RV contractility by presenting the relation between end-systolic area *versus* strain. For this purpose, we used the data before and after balloon inflation. We found an excellent correlation between the slopes of the end-systolic pressure area-relation *versus* strain area-relation (r=0.98, P<0.001). This observation provides further support for the ability of strain-area loops to assess RV cardiac function.

The non-invasive nature of the RV strain-area loop and its potential in assessing RV function and mechanics may contribute in evaluating and adjusting pharmacological therapy in pulmonary arterial hypertension patients, whereas right heart catherization is not ideal given its expensive, time-consuming and invasive nature. Further studies are warranted to better understand our observations, and to explore its potential (clinical) value.

Some caution must be taken when interpreting our results. The small sample size and limitations in deriving RV-area, further studies are warranted to explore and validate assessment of RV strain-area loops. Furthermore, this study is limited to patients with suspicion of PAH, therefore caution is needed in extrapolating findings to other populations. Importantly, also changes in pulmonary vascular resistance (because of preload manipulation) may contribute to our observations. For example, a decreased RV afterload (or pulmonary vascular resistance) is associated with an increase in RV longitudinal strain and *vice versa*. Measurement of pulmonary vascular resistance was not performed in this study.

In conclusion, this explorative study shows that a reduction in preload leads to a larger contribution of longitudinal myocardial strain to facilitate systolic volume ejection and *vice versa*. Most importantly, following comparison of the invasive RV strain-area and pressure-area loop, we found a strong correlation in the assessment of cardiac contractility. This suggests that both loops provide similar information, at least related to identification of loop shifts and cardiac contractility.

FIGURE LEGENDS

Figure 1. Mean RV strain-area (A), transformed strain-area (B) and RV pressure-area loops (C) of n=7 patients suspected of pulmonary arterial hypertension at baseline, after saline infusion and after IVC balloon inflation. For the transformed strain-area loop, positive instead of negative strain values are used-(B).

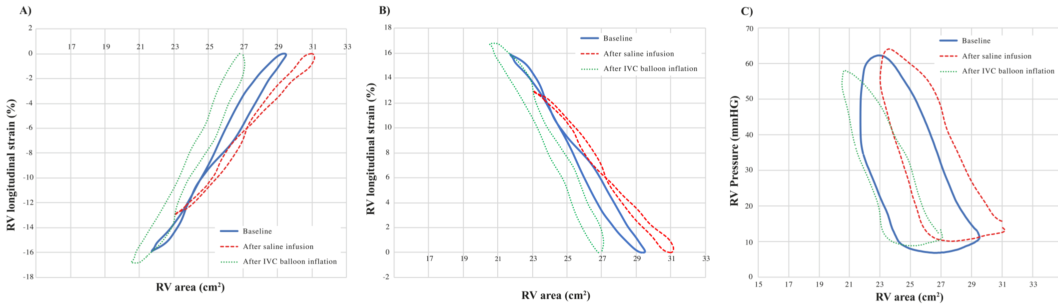
REFERENCES

[1] Oxborough D, Heemels A, Somauroo J, McClean G, Mistry P, Lord R, et al. Left and right ventricular longitudinal strain-volume/area relationships in elite athletes. Int J Cardiovasc Imaging. 2016;32:1199-211.

[2] Hulshof HG, van Dijk AP, George KP, Merkus D, Stam K, van Duin RW, et al. Echocardiographic-Derived Strain-Area Loop of the Right Ventricle is Related to Pulmonary Vascular Resistance in Pulmonary Arterial Hypertension. JACC Cardiovasc Imaging. 2017;10:1286-8.

[3] Hulshof HG, van Dijk AP, Hopman MTE, Heesakkers H, George KP, Oxborough DL, et al. 5-Year prognostic value of the right ventricular strain-area loop in patients with pulmonary hypertension. Eur Heart J Cardiovasc Imaging. 2020.

[4] Kleinnibbelink G, van Dijk APJ, Fornasiero A, Speretta GF, Johnson C, Hopman MTE, et al. Exercise-induced cardiac fatigue after a 45-minute bout of high-intensity running exercise is not altered under hypoxia. J Am Soc Echocardiogr - accepted. 2020.



A)
RV longitudinal strain (%)
RV area (cm²)
Baseline
After saline infusion
After IVC balloon inflation
B)
RV longitudinal strain (%)
RV area (cm²)
Baseline
After saline infusion
After IVC balloon inflation
C)
RV Pressure (mmHG)
RV area (cm²)
Baseline
After saline infusion
After IVC balloon inflation