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**Kleinnibbelink, G, Hulshof, HG, van Dijk, APJ, Cate, TT, George, KP, Oxborough, DL and Thijssen, DHJ (2020) Effects of preload manipulation on right ventricular contractility: invasive pressure-area loop versus non-invasive strain-area loop. Journal of the American Society of**

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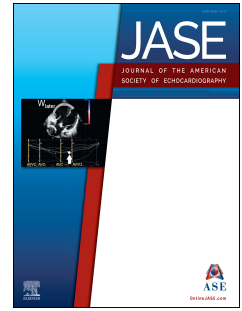
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# Journal Pre-proof

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

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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

Please cite this article as: Kleinnibbelink G, Hulshof HG, van Dijk APJ, Cate Tt, George KP, Oxborough DL, Thijssen DHJ, Effects of preload manipulation on right ventricular contractility: invasive pressure-area loop versus non-invasive strain-area loop, *Journal of the American Society of Echocardiography* (2021), doi: <https://doi.org/10.1016/j.echo.2020.12.007>.

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

3 **Brief title: RV function after preload manipulation**

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20  
21 **WORD COUNT:** 850

22 **FIGURES:** 1

23  
24  
25 **Funding:** This research did not receive any specific grant from funding agencies in the  
26 public, commercial, or not-for-profit sectors.

27 **Disclosures:** The authors have no relationships or conflicts to disclose

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

45  
46 We recruited 7 individuals (age 54±14 year, 71% female) undergoing right heart  
47 catheterisation (to diagnose pulmonary arterial hypertension). Participants provided informed  
48 consent prior to procedures. Study procedures were approved by local ethics committee  
49 (Radboudumc). During catheterisation a 24-mm AMPLATZER™ Sizing Balloon II (AGA  
50 Medical Corporation, Plymouth, USA) was introduced into the inferior vena cava for  
51 manipulation in preload. For direct time-point comparison between pressure, strain and area,  
52 we simultaneously recorded invasive RV pressure and 2D-echocardiographic images: 1) at  
53 baseline, 2) after intravenous infusion of 500ml saline (to increase preload), and 3) after intra-  
54 balloon inflation (to reduce preload). Echocardiographic data were analysed using QLAB  
55 V10.8 (Philips, Andover, USA) to measure RVLS and area (as previously described)<sup>3, 4</sup>,  
56 whilst RV pressure data were retrieved from Mac-Lab (GE Medical, Horton, Norway). After  
57 preload manipulation data were recorded within 1-minute after stabilization of the signal.

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

60

61 The increase in preload caused a rightward shift of the pressure-area loop, whilst a decrease  
62 in preload caused a leftward shift and reduced stroke volume. These characteristic shifts were  
63 also present in the strain-area loop, with an increase in preload inducing RV longitudinal  
64 strain decline and a decrease in preload causing an increase in peak RV longitudinal strain.  
65 The slope of the systolic phase of the strain-area loop (i.e.  $S_{slope}$ ) during preload elevation  
66 was significantly smaller than during preload reduction ( $-1.8 \pm 0.7\%/cm^2$  vs.  $-2.9 \pm 0.9\%/cm^2$ ,  
67  $P < 0.05$ ). A potential explanation of this finding is that as preload and stroke volume  
68 decreases there is a larger contribution of longitudinal fiber shortening with possible less  
69 dependency on circumferential fiber shortening to facilitate systolic volume ejection. This  
70 also may explain the paradoxical increase in peak longitudinal strain upon preload reduction  
71 as circumferential strain may be disproportionally decreased. Since we were not able to  
72 measure circumferential strain, this remains speculative. It is important to acknowledge the  
73 complexity of RV function, with changes in stroke volume potentially impacting upon  
74 various aspects of cardiac mechanics. This makes it difficult in our study to identify a single  
75 or most important factor explaining our observations.

76

77 Cardiac contractility is presented as the relation between end-systolic area (or volume) *versus*  
78 pressure. Using the non-invasive RV strain-area loop, we explored the ability to assess RV  
79 contractility by presenting the relation between end-systolic area *versus* strain. For this  
80 purpose, we used the data before and after balloon inflation. We found an excellent  
81 correlation between the slopes of the end-systolic pressure area-relation *versus* strain area-

82 relation ( $r=0.98$ ,  $P<0.001$ ). This observation provides further support for the ability of strain-  
83 area loops to assess RV cardiac function.

84

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

90

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

99

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

106 **FIGURE LEGENDS**

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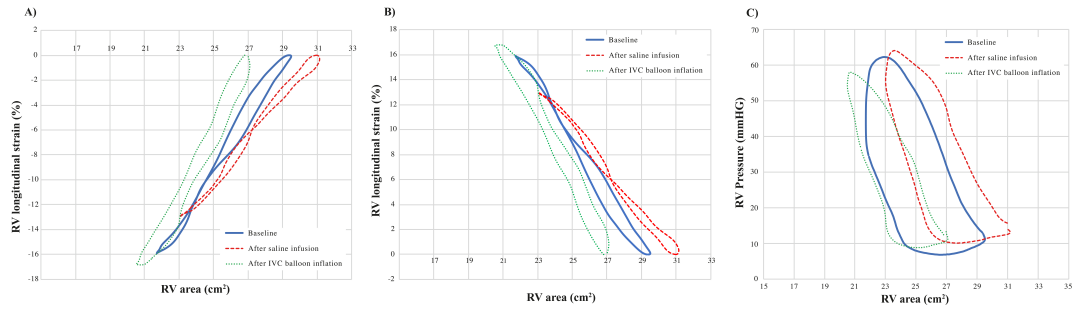
108 **Figure 1.** Mean RV strain-area (A), transformed strain-area (B) and RV pressure-area loops  
109 (C) of n=7 patients suspected of pulmonary arterial hypertension at baseline, after saline  
110 infusion and after IVC balloon inflation. For the transformed strain-area loop, positive instead  
111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

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