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Research letter

A pressure-based single beat method for estimation of right ventricular ejection fraction: Proof of concept

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Title: A pressure-based single beat method for estimation of right ventricular ejection fraction: Proof of concept.

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Summary: This proof of concept study suggests that estimation of RV ejection fraction based solely on analysis of the RV pressure waveform may be feasible.

Introduction

The utility of considering right ventricular (RV) contractility and afterload as independent entities and summarizing their balance or "coupling" using single beat methods has become widely appreciated[1-3]. Typically expressed as the ratio of end-systolic ventricular elastance (Ees, a load-independent measure of contractility), to arterial elastance (Ea, a lumped parameter measure of afterload) data suggest that when Ees/Ea reaches a critical threshold, the risk of cardiovascular decompensation begins to rise[4].

Pressure-based single beat methods have two central features: prediction of Pmax, the theoretical pressure generated within the RV if contraction remained isovolumic, and definition of end-systolic pressure (ESP). These variables are then used to calculate Ees as (Pmax- ESP)/stroke volume (SV), and Ea as ESP/SV. However, it remains unclear what a "normal" RV Ees/Ea value is, due in part to variation in how ESP is defined[5, 6] a consideration highlighted in a recent clinical study comparing single and multi-beat determination of Ees/Ea[7]. Additionally, directly relating Ees/Ea to RV ejection fraction (RVEF), a variable clinicians are more familiar with, is challenging. RVEF has been repeatedly shown to predict outcomes in patients with severe pulmonary hypertension (PH)[8], and while cardiac magnetic resonance imaging (cMRI) or 3D echocardiography allow for direct measurement of RVEF, they are not routinely used for repeated measurement of RVEF during a clinically indicated right heart study. The present proof of concept study was designed to test the hypothesis that a method using readily available software and based entirely on analysis of the RV pressure (RVP) waveform can effectively track acute changes in RVEF.

Methods

Archived measurements of RVP and RV volume provided by conductance/micromanometer catheter were retrospectively analyzed. Data had been acquired from 15 anesthetized swine (~55 kg)

under IACUC-approved protocols and in accordance with the NIH Guide for the Care and Use of Laboratory Animals. Input signals were sampled at 200 Hz and measured reference values for RVEF calculated from beat-to-beat RV volume as SV/end-diastolic volume. Data had been recorded before and during interventions to alter RV afterload alone or in combination with inotropic depression or augmentation.

The Dynamic Fit Wizard within SigmaPlot (version 13, Systat Software, Inc., San Jose, CA) was used to predict Pmax with a distribution function (the 4 parameter Weibull peak fit). In a pilot study involving 15 RVP waveforms with peak pressures ranging from ~20-50 mmHg the distribution function was found to yield Pmax values that were within 3$\pm$7 mmHg of those derived using a more conventional sinusoidal function (figure 1A). For EF estimation, an alternative approach for defining the RVP segments used in a Pmax prediction model was applied[9]. In addition, ESP was defined by approximating the point of maximal time varying RV elastance[10] using the second derivative of RVP (**figure 1B**). EF was then estimated as Ees/(Ees + Ea) (**figure 1C**). Since SV is a common factor in the calculation of both Ees and Ea, this equation can be reduced to (Pmax-ESP)/Pmax or further simplified to 1-(ESP/Pmax).

From the waveform library, a dataset containing 69 individual RVEF measurements was constructed and paired with EF estimates over the same sampling interval. Method comparison procedures were applied with and without adjustment for repeated measures and included scatter plots to describe correlation, Bland-Altman plots to define accuracy (bias) and precision (limits of agreement), and 4 quadrant concordance testing to determine uniformity of directional change. Estimated data were considered potentially interchangeable with measured values when the bias was $\leq$10% of the mean of all measured values, overall error (SD of the bias x 1.96/the mean of all EF values) was $\leq$30%, and concordance $\geq$90%.

Finally, preliminary clinical comparison of RVEF predicted from RVP recorded during diagnostic right heart catheterization (RHC) and that measured on the same day by cMRI was performed in six patients, three with pulmonary arterial hypertension and three with heart failure with preserved ejection fraction.

Results

RVEF estimation - experimental: Measured EF values ranged from 0.18 to 0.59 (mean 0.38±0.11), and estimated EF from 0.18 to 0.66 (mean 0.40±0.11). For all data, there was strong correlation (r^2 = 0.733, p<0.0001) with a bias of 0.03 (8% of mean) and limits of agreement from -0.9 to 0.13 (**figure 1D**). Overall error was 27%, and concordance 92% (plot not shown). When corrected for repeated measures (data not shown), correlation remained strong, (r^2 = 0.919, p<0.0001), bias was 0.02 (6% of mean) with limits of agreement from -0.03 to 0.07, overall error declined to 12.5%, and concordance improved to 100%.

RVEF estimation – clinical: Right ventricular EF measured by cMRI in six patients ranged from 0.30 to 0.70 and estimated EF from 0.32 to 0.64. The difference between estimated and cMRI-derived EF was ≤10% in all patients except for one with significant tricuspid regurgitation (estimated RVEF =0.38, cMRI RVEF = 0.70). However, estimated RV end-diastolic volume index in this patient (calculated as stroke volume index measured by indirect Fick/estimated EF) was virtually the same as that measured by cMRI (94 mL/m^2 vs 88 mL/m^2). This observation appears to reflect the fact that when measured by cMRI, RVEF represents both forward and regurgitant flow.

Discussion

Although RVEF and Ees/Ea derived from RVP waveforms and SV both represent the composite balance between contractility and afterload, defining a specific relationship between them is challenging. Results of this proof of concept study involving both experimental and clinical data support

the hypothesis that an alternative method for analyzing RVP waveforms can provide quantitative estimates of RVEF without measurement of RV volume.

The study is based on the premise that EF can be approximated within limits as Ees/(Ees+Ea) (figure 1C) then simplified to 1-(ESP/Pmax), a function similar to that previously described as an index of RV:PA coupling[11]. While this relationship removes the need for SV measurement, it is dependent upon consistent values for Pmax and ESP. When compared to conventional methods for Pmax prediction, preliminary data suggest our alternative approach produces similar results. In contrast, relative to the common practice of using mean pulmonary artery pressure as a surrogate for ESP, our method defines ESP in a manner more consistent with the point of maximal RV elastance[10].

Results of the study need to be interpreted in the context of limitations. Most importantly, as with single beat estimates of Ees based upon Pmax, the method assumes Vo of the end-systolic pressure volume relationship to be 0 mL[12] which is rarely true for either ventricle[13, 14]. While specific definition of how variation in Vo affects accuracy of pressure-based RVEF prediction remains to be determined, interventions known to affect Vo in swine are reflected in the experimental dataset [15], and the small clinical sample includes patients with PH, also shown be associated with a wide range of Vo[12]. Our study results indicate that despite variation in Vo, RVEF estimated by the pressure-based method reasonably approximated RVEF derived from direct measurements. These preliminary observations suggest that while a degree of Vo-dependence is inherent to the method, the error imparted by variation in Vo may not be prohibitive.

In summary, this proof of concept study suggests that estimation of RVEF may be feasible without measurement of RV volume. When combined with SV measurement, this method can allow for quantifying Ees and Ea as individual variables and specifically defining how alterations in each affected

an observed acute RVEF change during an intervention. These preliminary results support further validation studies.

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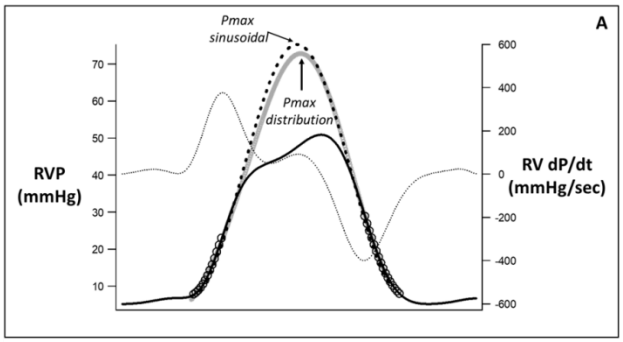
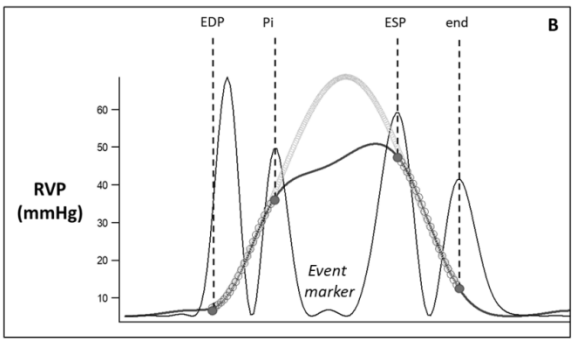
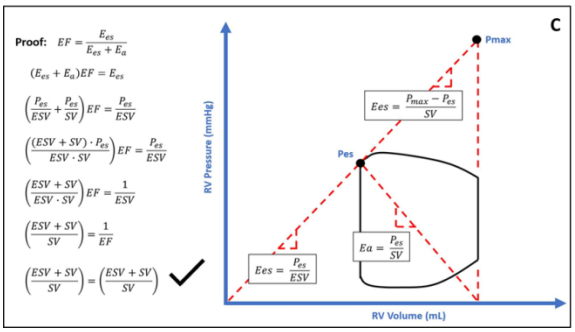
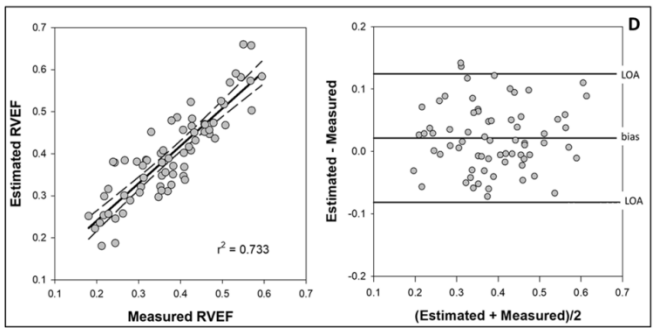
Figure legends:

Figure 1. Panel A. Comparison of Pmax predicted from laboratory data by application of conventional sinusoidal (hatched line) and Weibull distribution (solid gray line) functions using the same right ventricular pressure (RVP) segments (open circles superimposed on the solid black line depicting the RVP waveform). On average, Pmax values predicted by the distribution function were 3±7 mmHg lower than those predicted by the sinusoidal function. Panel B. For RVEF prediction, the signal average of a series of RVP waveforms was created (thick black line) and its second derivative squared to produce four upright peaks (thin black line labeled "Event marker"). These peaks were then used to define the "up and down" pressure segments for Pmax prediction (open circles and gray line, respectively) as the intervals from half of the first peak (end-diastolic pressure or EDP) to the second peak (the first inflection point or Pi), and from the third peak (end-systolic pressure or ESP) to the fourth (end). The third peak approximates the point of maximal time varying elastance with RVP at this point regarded as an estimate of true ESP. Panel C. Proof of the relationship EF=Ees/(Ees+Ea) in which both sides of the equation are resolved to the identical term. Panel D. Correlation between right ventricular ejection fraction (RVEF) directly calculated from continuous volume measurements as stroke volume/end-diastolic volume and RVEF estimated from the RVP waveform along with the Bland-Altman plot showing the mean difference between methods (bias) and the limits of agreement (LOA).


A
Pmax sinusoidal
Pmax distribution
RVP (mmHg)
RV dP/dt (mmHg/sec)
70
60
50
40
30
20
10
600
400
200
0
-200
-400
-600


B
EDP
Pi
ESP
end
RVP (mmHg)
Event marker
60
50
40
30
20
10


C
Proof: $EF = \frac{E_{es}}{E_{es}+E_a}$
$(E_{es}+E_a)EF = E_{es}$
$\left(\frac{P_{es}}{ESV}+\frac{P_{es}}{SV}\right)EF = \frac{P_{es}}{ESV}$
$\left(\frac{(ESV+SV)\cdot P_{es}}{ESV\cdot SV}\right)EF = \frac{P_{es}}{ESV}$
$\left(\frac{ESV+SV}{ESV\cdot SV}\right)EF = \frac{1}{ESV}$
$\left(\frac{ESV+SV}{SV}\right) = \frac{1}{EF}$
$\left(\frac{ESV+SV}{SV}\right) = \left(\frac{ESV+SV}{SV}\right)$
RV Pressure (mmHg)
RV Volume (mL)
Pmax
Pes
$Ees = \frac{P_{max}-P_{es}}{SV}$
$Ea = \frac{P_{es}}{SV}$
$Ees = \frac{P_{es}}{ESV}$


D
Estimated RVEF
Measured RVEF
r^2 = 0.733
Estimated - Measured
(Estimated + Measured)/2
LOA
bias
LOA