Right Ventricular Function in Heart Failure
The Long and Short of Free Wall Motion Versus Deformation Imaging

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It is well known that in pulmonary arterial hypertension, prognosis is determined by right ventricular (RV) function.[1] We are seeing more and more that in diverse conditions including congestive heart failure (HF), the RV tail is wagging the left ventricular dog.[2,3] The RV once again has been shown to be a major determinant of outcome, and as we refine our methods, our ability to prognosticate becomes more powerful. The next challenge is clarifying how best to assess RV function, and from this, how we can then use this technique to detect subtle, preclinical abnormalities and eventually have an impact on outcomes.

See Article by Carluccio et al

In this issue of *Circulation: Cardiovascular Imaging*, Carluccio et al[4] provide an elegant study demonstrating the superiority of RV free wall longitudinal strain (RVFWS) over tricuspid annular plane systolic excursion (TAPSE) for earlier detection of RV dysfunction, providing an ability to prognosticate and reclassify even in the setting of a guidelines-based normal TASPE value. Although this message can be diluted simply to let us do RV strain, there are several important messages that go well beyond this simple conclusion.

First, we must examine how shortening, measured by RVFWS, differs from longitudinal motion measured by TAPSE and why it better reflects function. Second, this study reiterates that some echo parameters seem to better predict outcomes than several clinical parameters, including age, sex, and even New York Heart Association class, and are complementary with incremental value to well-established HF risk scores. Finally, this study reinforces the concept that a normal value for an echocardiographic measure may not imply a good outcome and that prognostic cutoffs are not the same as cutoffs of so-called normalcy.

Why Might Free Wall Strain Be a Superior Method to Measure RV Function?

The RV assessment has long been one of the more challenging and technically difficult tasks in echocardiography. The complex and asymmetrical RV shape results in only limited segments being visible in any one acoustic imaging window, and imaging from several views is required to perform a complete evaluation, limiting the feasibility of comprehensive quantitative global and regional contractile functional assessment. Evaluation in the apical 4-chamber imaging window has become the most relied on view to perform such assessment and several quantitative parameters are available to augment visual evaluation. TAPSE (measured using M-mode imaging) is perhaps the most routinely used owing to its ease of measurement and reproducibility and its prognostic use. Evidence supports its value for predicting adverse outcomes in different HF populations and in other cardiovascular diseases.[2,5,6] However, TAPSE also has well-recognized limitations. TAPSE measures displacement of the fibrous tricuspid valve lateral annulus during systole and, therefore, is only a surrogate for global longitudinal RV function as it does not truly measure myocardial contraction nor take into account the presence of regional differences in function. Further, TAPSE is subject to the plane of M-mode imaging, a factor that may be particularly important in patients with significant RV dilatation who require a more lateral imaging plane position. Perhaps most importantly, TAPSE measures displacement and is therefore subject to translational error of cardiac motion, which can be influenced by several variables including heart rate, respiratory rate, chamber size, and body size. As a measure of deformation, strain analysis strives to provide a method of contractile function assessment that corrects for translational error and is less dependent on imaging plane angle. Two-dimensional RV systolic longitudinal strain calculated using speckle-tracking echocardiography has emerged as a feasible and reproducible measure of RV systolic function. Previous studies have demonstrated the superior prognostic use of RVFWS compared with TAPSE and other conventional echocardiographic parameters in patients with pulmonary arterial hypertension and other causes of HF.[7,8] The current study by Carluccio et al[4] in HF with reduced ejection fraction (HFrEF) patients with preserved TAPSE adds to this body of evidence, demonstrating RVFWS to be a more discriminating prognostic tool than other echocardiographic measures of RV function in HF patients.

Different factors contribute to the robustness of longitudinal RVFWS measurement. The predominance of longitudinally oriented deep RV myofibers supports RVFWS physiological suitability as a measure of RV function, and technically its measurement by speckle-tracking echocardiography involves tracking of acoustic markers in a relatively parallel alignment with ultrasound scan lines, allowing for more reliable tracking. Limitations of RVFWS include its relative dependence on image quality to ensure adequate tracking

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of myocardial acoustic markers, variability between different vendor software analysis systems, and a lack of normative data from large population-based studies. It is also worth noting that data are acquired from the apical 4-chamber view only, and so the contractile function of other RV regions may not be adequately represented. Advancements in strain analysis software systems have improved feasibility for use in clinical practice. With increasing clinical use, more data become available in different patient populations, and the value of strain for routine assessment of RV function becomes more evident. In this light, another commonly expressed technical consideration is that current 2-dimensional strain analysis software platforms (including the one used by Carluccio et al[4]) were designed to optimally track the bullet-shaped left ventricle and are adapted for use on the RV. Whether development of RV-specific 2-dimensional speckle-tracking echocardiography analysis software will enhance the use of RVFWS analysis is uncertain. Such limitations and questions will need to be addressed if RVFWS acceptance within the broader echocardiography community is to continue to grow.

RV Free Wall Strain to Predict Outcome

To test the association of RVFWS with the primary composite end point of death and HF hospitalization in a modest population size of HFrEF patients, Carluccio et al[4] used advanced statistical techniques to avoid overfitting of Cox proportional hazard modeling. They then used net reclassification improvement analysis to demonstrate the incremental prognostic value of RVFWS in comparison with validated HF risk prediction models including the EMPHASIS-HF score and the Echo-HF score.[9,10] The inclusion of validated prognostic risk scores in their modeling analysis is reassuring, as they provide a higher bar to demonstrate the value of RVFWS. The combining of imaging markers with clinical and laboratory parameters into validated HF clinical risk scores has become common, with inclusion of left ventricular EF in scores such as the Seattle Heart Failure Model providing a well-recognized example.[11] As cardiac imaging becomes more advanced and an indispensable component of HF patient assessment, it is anticipated that inclusion of other imaging parameters into such prognostic models will grow. More recent examples include the Echo-HF score, which uses only 5 echocardiographic parameters (including TAPSE) to predict survival for HFrEF patients, and the European Society of Cardiology/European Respiratory Society risk assessment score for pulmonary arterial hypertension, which includes assessment of right atrial area among clinical, laboratory, and hemodynamic variables.[12] To maintain their use and relevance, it is vital that such models are routinely updated to reflect modern advancements in HF patient evaluation. With an increasing pool of literature demonstrating the prognostic significance of RV function for different HF population, it begs the question as to whether incorporation of imaging-based measures of RV function such as RVFWS into existing or new clinical risk scores may provide incremental value. While beyond the scope of the current study, it presents a potentially important area for further research that could advance recognition of strain analysis' prognostic value and move it farther into the arena of routine clinical assessment. Before this can occur, many of the above-identified limitations of strain analysis would need to be definitively addressed, perhaps most important among them the issue of intervendor system variability.

Is Being Normal Sufficient?

The concept of 95% confidence intervals to determine reference limits and, therefore, to determine the so-called normalcy is a source of much controversy. Is normal simply a statistical determination based on a large, hopefully evenly distributed population. Alternately, should a value falling outside of this reference range of normal be necessarily prognostically relevant? The current article suggests that we must again challenge our concept of normal. We recently redefined our normal limits for EF, determining a lower reference limit of 53% based on the principle of 2 SDs from the mean.[13] This has now been applied arbitrarily for the sake of consistency to our definition of chemotherapy-induced cardiotoxicity,[14] despite outcomes data suggesting poorer prognosis with low normal left ventricular EF.[15] On the right side of the heart, we have seen several other examples of prognostic cutoffs being similar to, but not necessarily the same as the values recommended by guidelines or reference documents. In pulmonary arterial hypertension, for example, despite being within the reference limit for normal, a TAPSE of <1.8 cm imparts a 5.7-fold increase in mortality.[5] This is because the RV apex is very sensitive to afterload, while the base is the last to go.

In this current article, it is interesting to note that all included subjects had a guidelines normal TAPSE value, or a value that is within the 95th percent confidence limit. The fact that one could have a normal TAPSE and still have a poor prognosis as predicted by RV function tells us several things. First, recommendations for cutoff values do not impart normalcy but rather may be interpreted as there is a high likelihood that the value is abnormal if it falls outside of the reference range. Otherwise said, reference limits may be better at predicting abnormal as opposed to normal. Second, it informs us that not all recommended measures are equal. The mechanistic and methodologic differences between RVFWS and TAPSE explain why this is so. Finally, to advance the applicability of echo to provide clinically useful information, we must embrace the concept that different diseases cause different patterns of RV remodeling and we should choose the measure that best represents our ability to track these changes. Carluccio et al,[4] with this study, have done much to advance this concept by challenging the status quo and establishing new predictive prognostic values of RVFWS in HFrEF and by striving to detect dysfunction at earlier stages of disease.

So where are we left for RV function? Normal by any one measure does not necessarily mean good prognosis. In this study, simple longitudinal measures of motion did not fare well as a predictor of outcome and normal S' also did not impart a good prognosis, with similar values in those with and without clinical end points. Fractional area change, a more global measure of longitudinal and radial function, fares better. A strain above −15.3% yields the best fit to predict adverse outcomes with an area under the curve of 0.68, but to more accurately predict outcomes, echo parameters such as RVFWS must be added to established risk scores and vice versa with significant improvement in reclassification of risk. And finally,

this is not the ultimate answer. We need to apply this prospectively to a validation cohort, perhaps within risk prediction scores and models. In addition, we need to continue in our search for accurate means to assess the RV—3-dimensional volumes, EF, and strain and adjust them to the afterload they are facing. RV-guided therapy has been frustrating until now in the setting of HF,[16,17] but perhaps intervention at an earlier stage will yield dividends. Until then, as we have seen with other conditions, findings by Carluccio et al[4] suggests that we should move beyond a single simple measurement of function for such a complex chamber and routinely add free wall strain to our RV assessment in HFrEF patients. The long and short deformation imaging as measured by RVFWS is mechanistically more sound and clinically seems more useful than simple longitudinal excursion.

Disclosures

Dr Rudski—General Electric—has small stock holding outside of managed portfolio. The other author reports no conflicts.

References

1. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaïci A, Weitzenblum E, Cordier JF, Chabot F, Dromer C, Pison C, Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Cottin V, Degano B, Jaïs X, Montani D, Souza R, Simonneau G. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation*. 2010;122:156–163. doi: 10.1161/CIRCULATIONAHA.109.911818.
2. Ghio S, Recusani F, Klersy C, Sebastiani R, Laudisa ML, Campana C, Gavazzi A, Tavazzi L. Prognostic usefulness of the tricuspid annular plane systolic excursion in patients with congestive heart failure secondary to idiopathic or ischemic dilated cardiomyopathy. *Am J Cardiol*. 2000;85:837–842.
3. Ghio S, Guazzi M, Scardovi AB, Klersy C, Clemenza F, Carluccio E, Temporelli PL, Rossi A, Faggiano P, Traversi E, Vriz O, Dini FL; all Investigators. Different correlates but similar prognostic implications for right ventricular dysfunction in heart failure patients with reduced or preserved ejection fraction. *Eur J Heart Fail*. 2017;19:873–879. doi: 10.1002/ejhf.664.
4. Carluccio E, Biagioli P, Alunni G, Murrone A, Zuchi C, Coiro S, Riccini C, Mengoni A, D'Antonio A, Ambrosio G. Prognostic value of right ventricular dysfunction in heart failure with reduced ejection fraction: superiority of longitudinal strain over tricuspid annular plane systolic excursion. *Circ Cardiovasc Imaging*. 2018;11:e006894. doi: 10.1161/CIRCIMAGING.117.006894.
5. Forfia PR, Fisher MR, Mathai SC, Housten-Harris T, Hemnes AR, Borlaug BA, Chamera E, Corretti MC, Champion HC, Abraham TP, Girgis RE, Hassoun PM. Tricuspid annular displacement predicts survival in pulmonary hypertension. *Am J Respir Crit Care Med*. 2006;174:1034–1041. doi: 10.1164/rccm.200604-547OC.
6. Gorter TM, Hoendermis ES, van Veldhuisen DJ, Voors AA, Lam CS, Geelhoed B, Willems TP, van Melle JP. Right ventricular dysfunction in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *Eur J Heart Fail*. 2016;18:1472–1487. doi: 10.1002/ejhf.630.
7. Fine NM, Chen L, Bastiansen PM, Frantz RP, Pellikka PA, Oh JK, Kane GC. Outcome prediction by quantitative right ventricular function assessment in 575 subjects evaluated for pulmonary hypertension. *Circ Cardiovasc Imaging*. 2013;6:711–721. doi: 10.1161/CIRCIMAGING.113.000640.
8. Iacoviello M, Citarelli G, Antoncecchi V, Romito R, Monitillo F, Leone M, Puzzovivo A, Lattarulo MS, Rizzo C, Caldarola P, Ciccone MM. Right ventricular longitudinal strain measures independently predict chronic heart failure mortality. *Echocardiography*. 2016;33:992–1000. doi: 10.1111/echo.13199.
9. Collier TJ, Pocock SJ, McMurray JJ, Zannad F, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pitt B. The impact of eplerenone at different levels of risk in patients with systolic heart failure and mild symptoms: insight from a novel risk score for prognosis derived from the EMPHASIS-HF trial. *Eur Heart J*. 2013;34:2823–2829. doi: 10.1093/eurheartj/eht247.
10. Carluccio E, Dini FL, Biagioli P, Lauciello R, Simioniuc A, Zuchi C, Alunni G, Reboldi G, Marzilli M, Ambrosio G. The 'Echo Heart Failure Score': an echocardiographic risk prediction score of mortality in systolic heart failure. *Eur J Heart Fail*. 2013;15:868–876. doi: 10.1093/eurjhf/hft038.
11. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, Anand I, Maggioni A, Burton P, Sullivan MD, Pitt B, Poole-Wilson PA, Mann DL, Packer M. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation*. 2006;113:1424–1433. doi: 10.1161/CIRCULATIONAHA.105.584102.
12. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M, Aboyans V, Vaz Carneiro A, Achenbach S, Agewall S, Allanore Y, Asteggiano R, Paolo Badano L, Albert Barberà J, Bouvaist H, Bueno H, Byrne RA, Carerj S, Castro G, Erol Ç, Falk V, Funck-Brentano C, Gorenflo M, Granton J, Iung B, Kiely DG, Kirchhof P, Kjellstrom B, Landmesser U, Lekakis J, Lionis C, Lip GY, Orfanos SE, Park MH, Piepoli MF, Ponikowski P, Revel MP, Rigau D, Rosenkranz S, Völler H, Luis Zamorano J. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37:67–119. doi: 10.1093/eurheartj/ehv317.
13. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1.e14–39.e14. doi: 10.1016/j.echo.2014.10.003.
14. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, Ganame J, Sebag IA, Agler DA, Badano LP, Banchs J, Cardinale D, Carver J, Cerqueira M, DeCara JM, Edvardsen T, Flamm SD, Force T, Griffin BP, Jerusalem G, Liu JE, Magalhães A, Marwick T, Sanchez LY, Sicari R, Villarraga HR, Lancellotti P. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2014;27:911–939. doi: 10.1016/j.echo.2014.07.012.
15. Romond EH, Jeong JH, Rastogi P, Swain SM, Geyer CE Jr, Ewer MS, Rathi V, Fehrenbacher L, Brufsky A, Azar CA, Flynn PJ, Zapas JL, Polikoff J, Gross HM, Biggs DD, Atkins JN, Tan-Chiu E, Zheng P, Yothers G, Mamounas EP, Wolmark N. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol*. 2012;30:3792–3799. doi: 10.1200/JCO.2011.40.0010.
16. Bonderman D, Ghio S, Felix SB, Ghofrani HA, Michelakis E, Mitrovic V, Oudiz RJ, Boateng F, Scalise AV, Roessig L, Semigran MJ; Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension Riociguat Trial (LEPHT) Study Group. Riociguat for patients with pulmonary hypertension caused by systolic left ventricular dysfunction: a phase IIb double-blind, randomized, placebo-controlled, dose-ranging hemodynamic study. *Circulation*. 2013;128:502–511. doi: 10.1161/CIRCULATIONAHA.113.001458.
17. Tedford RJ, Hemnes AR, Russell SD, Wittstein IS, Mahmud M, Zaiman AL, Mathai SC, Thiemann DR, Hassoun PM, Girgis RE, Orens JB, Shah AS, Yuh D, Conte JV, Champion HC. PDE5A inhibitor treatment of persistent pulmonary hypertension after mechanical circulatory support. *Circ Heart Fail*. 2008;1:213–219. doi: 10.1161/CIRCHEARTFAILURE.108.796789.

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