Editorial

Regional Myocardial Contractility
The Elusive Phantom of Cardiology

Frank E. Rademakers, MD, PhD

The characterization of myocardial function, both on the global but even more so on the regional level, remains an elusive art in cardiology—the holy grail for clinicians and researchers alike. Left ventricular (LV) ejection fraction (EF) is being widely used to define global function but has several drawbacks. As a ratio between stroke volume (SV) and end-diastolic volume (EDV), the interpretation of abnormal values or of changes in EF can be difficult or even misleading. Because the function of the ventricle is the delivery of blood to the circulation/organs at an adequate arterial pressure, SV is the more relevant parameter for ventricular function, certainly if measured at rest and during stress/exercise. But both a low and a high EF can deliver such an adequate SV wholly depending on the size of the ventricle, that is, EDV: a large ventricle does not require a high EF to deliver an adequate SV; similarly in normal ventricles as witnessed by the athlete's heart. On the contrary, a small ventricle (low EDV) will require a high EF to deliver an adequate SV, with possible diastolic problems in consequence. The dependence of EF on loading conditions is another major issue in its interpretation, and the inclination to equate EF with intrinsic contractility is thus completely flawed.[1]

See Article by Espe et al

When the ventricle is damaged by a myocardial infarction (MI), the interpretation of myocardial function becomes even more difficult because variable compliance of tissue, bulging, and electric and mechanical dyssynchrony create internal shifts in blood, which, much as in mitral insufficiency, change the relationship between myocardial deformation and forward SV. Here, the evaluation of regional function becomes even more important.

In this issue of the journal, Espe et al[2] report on a study of regional function after an MI in 62 rats (and 14 sham controls) using cine and phase-contrast magnetic resonance imaging. They divided the MI rats into 2 groups depending on end-diastolic LV pressure (threshold 15 mm Hg) as failing or nonfailing. They observed increased work and preserved longitudinal strain (as compared with sham) in the myocardium remote from the MI in the nonfailing hearts, whereas strain was decreased and regional work did not increase in the failing hearts. In the region adjacent to the MI, the main observation was reduced work in the failing ventricles related to high levels of negative work. Overall, the calculation of work offered better insights than strain alone.

The reaction of the remote, normal myocardium (in the case where there is no epicardial coronary abnormality) to the problem of a loss of contractile force of the ventricle because of an MI, has been subject to a longstanding debate and several concepts are continuously being challenged. Is there really compensatory hypertrophy in the remote myocardium? If so, is this because of myocardial cell hypertrophy or interstitial fibrosis or both? Is the intrinsic contractility of the remote myocardium normal? If it is decreased, is this because of cellular abnormalities,[3] abnormal innervation,[4] or changes in blood supply because of endothelial dysfunction or other mechanisms?[5]

Espe et al[2] have provided some pieces of this puzzle by performing this difficult study involving an intricate methodology combining high-field (9.4 T) magnetic resonance cine but also phase contrast, with pressure measurements and Doppler flow in rats. The overarching conclusion of their study is that nonfailing rats have better function with more work being performed in the remote myocardium, whereas failing rats lack this compensation.

The authors are to be commended for the performance of this complex study, combining several methodologies, to unravel the consequences of a loss of regional contractile force on the remaining segments of the LV. They have brought several novel methods and concepts into this field, including the use of phase-contrast magnetic resonance to calculate regional strains and the calculation of regional work, including wasted work.

On the contrary, as with any type of innovative work, some concerns and caveats can be raised.

One of them is that failure is defined as increased diastolic LV pressure and congestion, which is a diastolic or filling problem, whereas systolic performance as witnessed by SV is identical in shams, failing, and nonfailing rats. The lower cardiac output in failing rats is only because of a lower heart rate—an observation which is difficult to explain in this context and for which the authors do not provide an explanation.

Some of the phrasing of the authors indicates that they perceive higher work as a good thing and that work is load independent. Neither of these is necessarily true.

Work is defined in this study as the multiplication of LV pressure, radii of curvature, and the temporal derivative of area strain; because the authors have also calculated myocardial

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Department of Cardiovascular Sciences, University Hospitals Leuven, KU Leuven, Belgium.

Correspondence to Frank E. Rademakers, MD, PhD, KU Leuven Department of Cardiovascular Sciences, University Hospitals Leuven, AD04 Herestraat 49, Leuven 3000, Belgium. E-mail frank.rademakers@med.kuleuven.be

(*Circ Cardiovasc Imaging*. 2017;10:e006906. DOI: 10.1161/CIRCIMAGING.117.006906.)

***Circ Cardiovasc Imaging* is available at http://circimaging.ahajournals.org**

DOI: 10.1161/CIRCIMAGING.117.006906

stress incorporating wall thickening, this could also have been used for the calculation of work. It would have been even better to use the full deformation of the wall, including all measured strains.[6] Irrespective of the components of the strain calculation, stroke work itself has been shown to be load dependent.[7] A load-independent parameter of ventricular performance is the slope of the end-ejection stress–strain (pressure–volume) relationship or preload recruitable stroke work[8] where the slope between stroke work and EDV is calculated. Because the authors have stress–strain curves from different areas of the same ventricle they could have calculated the end-ejection slope of these different curves as described in Jasaityte et al.[9] This assumes the same contractility in these different segments but, given this limitation, could have provided a better measure of true intrinsic contractility and offered the opportunity to detect the presence or not of enhanced contractility in these remodeled ventricles and a possible difference between the failing and nonfailing rats. Now we can only evaluate the difference in work, which is mainly driven by loading conditions which are different between the various regions and between the failing and nonfailing rats, as shown and discussed by the authors.

An increase in work normally coincides with increased oxygen consumption and metabolic activity. Although this was not measured directly as mentioned in the limitations, this is probably the case and cannot be viewed as positive per se, certainly in view of the observed similar SV in the sham and MI ventricles. It is clear that the congestive heart failure rats have more problems as witnessed by their increased end-diastolic pressure and lung weight, but these are diastolic problems. Failing ventricles have maintained their SV through higher LV EDV and thus lower EF at the expense of higher filling pressures, whereas nonfailing ventricles have maintained SV with less increased EDV and thus higher EF but at the expense of higher work (and probably thus oxygen consumption and metabolism).

From a clinical perspective, one can rightfully argue that the nonfailing situation is to be preferred, but the increased work which is observed in the nonfailing rats can also have negative consequences in the longer run. In this regard, a longer follow-up with measurements at different time points could be helpful, but in view of the complexity of the methodology, this is clearly difficult to obtain.[10]

The added value of the calculation of derived work parameters, that is, besides work per unit surface area also work per unit of long-axis length and per mass, is unclear because the calculation of work to start with is complex and becomes even more challenging to interpret with the various definitions; when work is calculated over a different area in the sham animals (to match with different regions in the MI rats), this yields a significantly different result[2] (Figure 4B and 4C in the study by Espe et al) illustrating the sensitivity of the method to how the parameter is defined and calculated. The results and interpretation are also different if one observes work per unit surface area versus work per unit of mass. We should, therefore, be cautious to over interpret small differences in regional work.

The authors make a strong case about the role of wasted regional deformation. This concept existed already but is nicely illustrated in this study, and it is clear that more deformation and work is wasted in the failing ventricles with larger infarcts and larger EDVs. Assuming that the tissue in the adjacent segments is intrinsically similar to that in the remote territory, the higher waste is probably because of tethering of this adjacent segment to the infarcted scar area, which in a rat model is typically thin and stretches with each systole, more so than in most human infarcts. The lower deformation in these adjacent segments could easily be interpreted as an intrinsic abnormality of the tissue, possibly because of remaining ischemia, but although such intrinsic abnormality cannot be completely excluded in this study, it most probably due to the higher loading conditions. This should caution clinicians not to over interpret abnormal regional function, that is, deformation, in segments neighboring an infarct because deformation alone cannot distinguish between loading as the cause versus contractility decrease through ischemia or replacement fibrosis. Given the loss of coherence of deformation in the congestive heart failure rats, the interaction of SV with the peripheral circulation will also vary, with variations in timing of peak loading. This can by itself produce abnormalities in timing and extent of deformation because the ventricle and the aorta are coupled and interact continuously throughout the entire period of ejection, which can even have marked effects on diastolic function.[11]

Another interesting observation[2] (Figure 3B in the study by Espe et al) is the lower longitudinal strain in the remote zone of the failing larger ventricles. The shape changes consequent to the large bulging infarcts could increase the stretch/load on the normal segments in the longitudinal direction much like pushing on the lid of a cylinder increases the stress in the walls of the cylinder, but only in the long axis, leaving circumferential shortening less affected.[12] It requires further study to really prove this hypothesis, but it could be an explanation why the location and extent of an infarct together with the overall shape could have differential effects on remote myocardium.[13]

As with every well-performed study in a complex setting, results are sometimes difficult to interpret and give rise to variable interpretations. The topic is, however, important in view of the increasing numbers of people surviving a myocardial infarct but evolving into heart failure without an accurate way to predict who will and who will not show such an evolution.[14] Studies like this one are, therefore, important to further our insights into the mechanisms of remodeling.

Disclosures

None.

References

1. Konstam MA, Abboud FM. Ejection fraction: misunderstood and overrated (changing the paradigm in categorizing heart failure). *Circulation*. 2017;135:717–719. doi: 10.1161/CIRCULATIONAHA.116.025795.
2. Espe EKS, Aronsen JM, Eriksen M, Sejersted OM, Zhang L, Sjaastad I. Regional dysfunction after myocardial infarction in rats. *Circ Imaging*. 2017;10:e005997. doi: 10.1161/CIRCIMAGING.116.005997.
3. Gallagher G, Menzie S, Huang Y, Jackson C, Hunyor SN. Regional cardiac dysfunction is associated with specific alterations in inflammatory cytokines and matrix metalloproteinases after acute myocardial infarction in sheep. *Basic Res Cardiol*. 2007;102:63–72. doi: 10.1007/s00395-006-0610-7.
4. Gimelli A, Masci PG, Liga R, Grigoratos C, Pasanisi EM, Lombardi M, Marzullo P. Regional heterogeneity in cardiac sympathetic innervation in acute myocardial infarction: relationship with myocardial oedema on

magnetic resonance. *Eur J Nucl Med Mol Imaging*. 2014;41:1692–1694. doi: 10.1007/s00259-014-2792-9.
5. Münzel T, Camici GG, Maack C, Bonetti NR, Fuster V, Kovacic JC. Impact of oxidative stress on the heart and vasculature: part 2 of a 3-part series. *J Am Coll Cardiol*. 2017;70:212–229. doi: 10.1016/j.jacc.2017.05.035.
6. Rademakers F, Van de Werf F, Mortelmans L, Marchal G, Bogaert J. Evolution of regional performance after an acute anterior myocardial infarction in humans using magnetic resonance tagging. *J Physiol*. 2003;546(pt 3):777–787.
7. Theroux P, Ross J Jr, Franklin D, Covell JW, Bloor CM, Sasayama S. Regional myocardial function and dimensions early and late after myocardial infarction in the unanesthetized dog. *Circ Res*. 1977;40:158–165.
8. Glower DD, Spratt JA, Snow ND, Kabas JS, Davis JW, Olsen CO, Tyson GS, Sabiston DC Jr, Rankin JS. Linearity of the Frank-Starling relationship in the intact heart: the concept of preload recruitable stroke work. *Circulation*. 1985;71:994–1009.
9. Jasaityte R, Claus P, Teske AJ, Herbots L, Verheyden B, Jurcut R, Rademakers F, D'hooge J. The slope of the segmental stretch-strain relationship as a noninvasive index of LV inotropy. *JACC Cardiovasc Imaging*. 2013;6:419–428. doi: 10.1016/j.jcmg.2012.10.022.
10. Mann DL, Foale RA, Gillam LD, Schoenfeld D, Newell J, Weyman AE. Early natural history of regional left ventricular dysfunction after experimental myocardial infarction. *Am Heart J*. 1988;115:538–546.
11. Chirinos JA, Phan TS, Syed AA, Hashmath Z, Oldland HG, Koppula MR, Tariq A, Javaid K, Miller R, Varakantam S, Dunde A, Neetha V, Akers SR. Late systolic myocardial loading is associated with left atrial dysfunction in hypertension. *Circ Cardiovasc Imaging*. 2017;10:e006023. doi: 10.1161/CIRCIMAGING.116.006023.
12. Bell V, Mccabe EL, Larson MG, Rong J, Merz AA, Osypiuk E, Lehman BT, Stantchev P, Aragam J, Benjamin EJ, Hamburg NM, Vasan RS, Mitchell GF, Cheng S. Relations between aortic stiffness and left ventricular mechanical function in the community. *J Am Heart Assoc*. 2017;6:e004903. doi: 10.1161/JAHA.116.004903.
13. Bogaert J, Bosmans H, Maes A, Suetens P, Marchal G, Rademakers FE. Remote myocardial dysfunction after acute anterior myocardial infarction: impact of left ventricular shape on regional function: a magnetic resonance myocardial tagging study. *J Am Coll Cardiol*. 2000;35:1525–1534.
14. Wang N, Hung CL, Shin SH, Claggett B, Skali H, Thune JJ, Køber L, Shah A, McMurray JJ, Pfeffer MA, Solomon SD; VALIANT Investigators. Regional cardiac dysfunction and outcome in patients with left ventricular dysfunction, heart failure, or both after myocardial infarction. *Eur Heart J*. 2016;37:466–472. doi: 10.1093/eurheartj/ehv558.

KEY WORDS: Editorials ■ arterial pressure ■ myocardial infarction ■ myocardium ■ stroke volume

Regional Myocardial Contractility: The Elusive Phantom of Cardiology

Frank E. Rademakers

Circ Cardiovasc Imaging. 2017;10:
doi: 10.1161/CIRCIMAGING.117.006906
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-9651. Online ISSN: 1942-0080