



Research Direction at Our Lab

Biederman RW*

Department of Cardiology, Temple University School of Medicine, USA

Editorial

At our cardiac magnetic resonance (CMR) imaging lab we have a clinical throughput that exceeding 1000 studies a year. By radiologic standard this number may seem very low, but by CMR standards this is at the upper end of performance. With our exclusive focus on addressing cardiology issues or imaging patients with cardiac complications (such as possessing a pacemaker) this makes our lab among only a few in the world with such a heavy focus on cardiovascular diseases. In fact, it used to be said that cardiac studies comprised less than 4% of all MRI cases globally, but today that percentage is a lot smaller, in part because of the rapidly growing role that MRI plays in radiology, and also due to the much slower adoption of MRI for cardiovascular diseases. Our research focus is directed at finding a clinical utility for CMR that brings it in line with other body regions, where MRI has become the dominant modality in many cases. This is not driven by an MRI-centric view of the world where “MRI for the sake of MRI” guides our thought process, but simply recognition that in many areas, with the glaring exception of cardiovascular disease, the use of MRI has resulted in great value to the patient, the medical community and society at large. The lack of applicability to CV disease is partly due to the richness of modalities directed at cardiovascular disease and partly due to the fact that MRI has generally failed to provide a unique benefit for CV disease. Possibly, one exception to this is the utility of gadolinium enhancement, with late enhancement delineating the extent of myocardial fibrosis and early enhancement delineating the extent of myocardial tissue edema associated with a myocardial infarction or infection. However, these are diagnostic signs that materialize after an event, and much of mainstream cardiovascular imaging (non-MRI) is directed at preventing the occurrence of a myocardial infarction via early detection followed by an appropriate intervention. To this end, the mainstream CV modalities focus in one form or another on the condition of the coronary arteries, either by direct visualization or indirectly by provoking a response in myocardial perfusion or wall motion. While CMR can mimic some of these modalities there has been little success in demonstrating a dominant advantage of MRI, given its low throughput, high expense and general reliance on the same physiology that other modalities seek to exploit, often with greater specialization and more appropriate resolution, both spatially and temporally.

OPEN ACCESS

*Correspondence:

*Biederman RW, Director, Department of Cardiology, Temple University School of Medicine, 320 E. North Avenue, USA,
Tel: 412-359-8705;*

E-mail: Robert.Biederman@ahn.org

Received Date: 15 Jul 2017

Accepted Date: 28 Aug 2017

Published Date: 04 Sep 2017

Citation:

Biederman RW. Research Direction at Our Lab. J Heart Stroke. 2017; 2(6): 1038.

ISSN: 2475-5702

Copyright © 2017 Biederman RW. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

With this as background, we focused our CMR research on a general approach that could make an immediate and significant difference to patient outcomes. However, given the low adoption rate of CMR, this is only feasible if MRI is used to fundamentally better understand CV disease and can be used to point to a more appropriate use of existing modalities (including CMR) to allow CV disease to be better addressed. Before we delineate our CMR research focus, it is necessary to visit some alarming background information. It cannot have escaped anyone’s notice that there has been a paucity of “wins” in the last decade for the pharmacological or device industry in the fight against CV disease. Consider the near-collapse of many major pharmaceutical companies as they fell off the “patent cliff” after about 20 years of block-buster cardiac medicines, when they were left with few new drugs and while CV disease continued to be the dominant disease leading. Further, consider the decade-old COURAGE trial that showed that there was no benefit to percutaneous coronary artery intervention compared to optimal medical treatment [1]. Further studies, including the FAME I or II trials that sought to guide PCI via fractional flow reserve considerations have not convincingly overturned this verdict (since there was no trail arm without PCI performed). There is now some indication that guiding PCI by cath lab measured FFR is potentially harmful, as evidenced by the early termination of the recent FUTURE trial [2]. Thus, this mainstay of treatment of coronary artery disease has long been reduced to alleviating angina symptoms rather than preventing events. Possibly, doubts concerning the utility of PCI may have contributed to over a decade-long decline in the percentage of patients sent to the cath lab form myocardial perfusion testing labs, such as nuclear SPECT, PET and even from newer technologies such as CTA [3]. Indeed, the organizers of the SPARC trial that tested the utility of these three modalities under clinical conditions anticipated

that 40% of patients with suspected CAD disease would be sent to the cath lab, only to find that about 5-10% of patients were sent [4]. Unless SPECT and other labs are inundated by patients by a factor of 8 compared to historical levels then these modalities are systematically underestimating the presence of CAD. An argument against this is that historically, the percentage of patients presenting at the cath lab without any significant CAD has continued to be about 40% to 60%, with the (unstated) implication that the sensitivity is sufficiently high so as not to miss disease (due to the high rate of overcalling disease). However, it can be easily shown that for a population with about 25% disease, that a low sensitivity (<50%) and high specificity (>85%) can result in this mix of patients at the cath lab. In fact, economic forces (as shown in the SPARC trial) discourage increasing the sensitivity but encourage increasing specificity. To be economically feasible, a modality has to either simultaneously possess a high sensitivity and a high specificity or failing this, with only a moderate response on the receiver-operator curve (ROC) it has to increase its specificity at the expense of lowering sensitivity, which is consistent with the long-term decline in percentage of patients sent to the cath lab.

It has long been acknowledged that CMR is rich in parameters and can mimic the performance of other modalities, hence the much attempted approach of using CMR to duplicate the role of other modalities. Instead, we took a different approach and recognized that there is much to be learned when modalities are compared. For instance, in the Women's Ischemia Syndrome Evaluation (WISE) we compared CMR myocardial perfusion with nuclear SPECT perfusion. Initially, the intent was to determine if CMR was superior to SPECT, but (as has been shown by several subsequent trials) there is no clear win for CMR when considering the combination of sensitivity, specificity and patient throughput [5]. Our subsequent approach went beyond this initial performance comparison and compared the details of the CMR data with SPECT data and identified certain characteristics of each modality that allowed the performance of each modality to be improved [6]. That is, the formal and detailed comparison of two modalities showed that certain physical characteristics of the patient and imaging modality masked the presence of disease. This masking generally resulted in lowering sensitivity and specificity. We showed that when these physical features are correctly taken into consideration for each modality, the data can better identify the presence of disease [7]. To date, we have demonstrated that sensitivity can be dramatically improved, while not harming specificity. Future work will extend this approach to also improving specificity, and hopefully move diagnostic modalities to economically sustainable high levels of sensitivity. Counter intuitively, we exploited this feature rich CMR examination and comparison to also improve nuclear SPECT! However, we also showed how CMR can better interpret myocardial perfusion data, which leaves both modalities free to incorporate these findings in their reading of data and in the design of future scanners. It has often been observed (especially in a fast changing modality such as echocardiography) that when new technical features are made available, they are often discarded due to lack of clinical benefit. This necessarily slows down the introduction of new capabilities, as manufacturers fail to realize commercial benefit for their efforts and ingenuity. We know of no reason why our approach of unveiling hidden impediments to diagnostic image interpretation cannot be extended to other modalities and to other diagnoses, which may well precipitate acceleration of scanner capabilities as hidden constraints are progressively removed. Naturally, it is our hope that CMR is among the beneficiaries of this.

Just as the comparison between CMR and SPECT revealed a feature of fundamental benefit, another area of our research focus may also have uncovered a previously hidden feature that has potential to alter our perception and treatment of CV disease. We identified as a study area the shortcomings of assessing left ventricular ejection fraction by CMR. It has been shown that reproducibility of CMR measured EF is at best approximately 5% [8]. With the implication that the true EF falls in a range +10% to -10% of the measured EF 95% of the time, which is a large margin of error when considering that a series of interventional procedures are triggered at a series of sharp EF thresholds. Further, the reproducibility error of measuring EF from a fixed data set is not the full extent of potential sources of error, since in a multiple breath hold study, reproducibility of the breath hold position may add considerably to sources of error in measuring EF. When one adds in the potential sources of error of accommodating papillary muscles, trabeculae and selection of the correct basal plane at end diastole and end systole (typically adjusted by one whole slice thickness), it can be seen that any volumetric approach has significant drawbacks, and attempts to compensate inevitably add time and expense to the acquisition or processing of data. Instead, our approach focused on conditions of LV outflow through the aorta. By placing a phase velocity scan across the aorta, we can quantitatively measure blood flow exiting the LV. Initially, this was to be used to confirm the stroke volume measured by volumetric means and then attempt to correct the volumetric data based on the two independent measures of output. However, further examination of the data revealed that there was a systematic variation in the flow pattern with ejection fraction. Investigation of this phenomena lead to the formulation of an impedance index that is measured from the time-resolved aortic blood waveform, and we showed how it can be related to EF via a simple formula [9]. Importantly, we showed that this impedance index exhibited a periodic variation over a wide range of EF values that was characteristic of a resonance system. The implication is that if ejection of blood into the vasculature is characterized by resonance conditions, then there should be a penalty for operating off resonance. Our initial data suggested that this was indeed the case with adverse cardiovascular events did exhibiting the periodic intensification that such a resonance system indicates. The repercussions of this are important in that we could explain the cardiovascular event rate without recourse to any of the usual variables such as coronary artery stenosis, perfusion level, co-morbidities, medication, treatments, and so on. That is not to say that these other features are not important, but that the CV resonance condition may be a dominant driver of events that modifies the influence of other conditions and treatments. We believe that the resonance phenomena exhibited by the CV system has potential to provide an explanatory context for guiding therapy and prognostication. While the flow data required for this measurement could conceivably be derived using echocardiography, this has yet to be established, and currently, only CMR can provide the necessary data in a rapid manner (in one minute of scanning) [10]. Thus, the stage may be set to allow CMR to achieve a mainstream measurement with the necessary accuracy and rapidity of throughput to make it feasible for widespread use. More importantly, the resonance view of the CV system could be the break-through insight that allows the full might of industry and academia to once again, make valuable inroads in fighting CV disease.

To end on a philosophical note, our general approach to research involved questioning the assertion that CMR or any modality is the true gold standard for measurement in light of the vast expanse of

burden of unresolved CV disease, and recognizing that the CV community has been gradually losing, not gaining, tools to fight this dominant disease process.

References

1. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med.* 2007;356(15):1503-16.
2. Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol.* 2010;56(3):177-84.
3. Rioufol G, Mewton N, Rabilloud M, editors. The functional testing underlying coronary revascularization (FUTURE) study: a "real world" comparison of fractional flow reserve-guided management vs conventional management in multi vessel coronary artery disease patients. The 2016 American Heart Association Scientific Sessions; 2016; November 12-16, New Orleans, LA.
4. Rozanski A, Gransar H, Hayes SW, Min J, Friedman JD, Thomson LE, et al. Temporal trends in the frequency of inducible myocardial ischemia during cardiac stress testing 1991 to 2009. *J Am Coll Cardiol.* 2013;61(10):1054-65.
5. Hachamovitch R, Nutter B, Hlatky MA, Shaw LJ, Ridner ML, Dorbala S, et al. Patient management after noninvasive cardiac imaging results from SPARC (Study of myocardial perfusion and coronary anatomy imaging roles in coronary artery disease). *J Am Coll Cardiol.* 2012;59(5):462-74.
6. Greenwood JP, Maredia N, Younger JF, Brown JM, Nixon J, Everett CC, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. *Lancet.* 2012;379(9814):453-60.
7. Doyle M, Pohost GM, Merz CNB, Shaw LJ, Sopko G, Rogers WJ, et al. Improved diagnosis and prognosis using decisions informed by combining entities (DICE): results from the NHLBI-sponsored women's ischemia syndrome evaluation (WISE). *Cardiovasc Diagn Ther.* 2013;3(4):216-27.
8. Doyle M, Pohost GM, Bairey Merz CN, Shaw LJ, Sopko G, Rogers WJ, et al. Use of bio-informatics assessment schema (BIAS) to improve diagnosis and prognosis of myocardial perfusion data: results from the NHLBI-sponsored women's ischemia syndrome evaluation (WISE). *Cardiovasc Diagn Ther.* 2016;6(5):424-31.
9. Suinesiaputra A, Bluemke DA, Cowan BR, Friedrich MG, Kramer CM, Kwong R, et al. Quantification of LV function and mass by cardiovascular magnetic resonance: multi-center variability and consensus contours. *J Cardiovasc Magn Reson.* 2015;17(1):63.
10. Doyle M, Pohost GM, Merz CNB, Shaw LJ, Sopko G, Rogers WJ, et al. Aortic flow conditions predict ejection efficiency in the NHLBI sponsored women's ischemia syndrome evaluation (WISE). *Cardiovasc Diagn Ther* 2017;7(3):288-95.