A Novel Index of Remodeling in Hypertensive Heart Disease

Gerard P. Aurigemma, MD; Michael Salerno, MD, PhD, MS

Left ventricular hypertrophy (LVH) is thought to be an adaptive response that allows for normal ejection fraction despite abnormal pressure or volume load, or a combined pressure and volume load.[1] However, this adaptation is associated with substantially increased morbidity and mortality.[2] Echocardiography helped create the dossier on the prevalence and consequences of LVH in hypertension and outcome response to treatment.[3,4] Echocardiography and now cardiac magnetic resonance imaging (CMR), a more precise means to measure LVH, have been used in cross-sectional and epidemiological studies and serially in clinical trials.[4,5]

See Article by Goh et al

LVH, which is most properly defined as an increase in left ventricular (LV) mass in relation to body size (ie, high LV mass index),[4,6] is produced either by an abnormal increase in chamber size, an abnormal increase in wall thickness, or abnormal increases in both. In general, in LVH, higher than expected LV wall thickness is associated with a normal end-diastolic volume.[7] For decades, concentric hypertrophy—an abnormally high LV wall mass and an abnormally high ratio of LV wall thickness/the size of the LV cavity—was thought to be the most common response pattern to chronic pressure overload.

A major conceptual advance in our thinking about the LV response to pressure overload occurred a quarter-century ago when the Cornell group published a simple quantitative classification paradigm based on standard linear echocardiographic data in a study of untreated hypertensive patients.[8] They categorized the LV response to hypertension based on partition values for (1) the LV mass indexed to body surface area and (2) the ratio of LV wall thickness/LV chamber size—the geometry of the LV, or the relative wall thickness (RWT). In this scheme, there were 4 possible geometry/hypertrophy combinations: normal LV mass index and normal RWT; concentric LVH; elevated LV mass index and high RWT; eccentric LVH; high LV mass index with normal RWT; and concentric remodeling, a term they introduced, was defined as an elevated RWT without LVH. Interestingly, in this and other studies, the majority of the hypertensive patients had neither hypertrophy nor concentric geometry.

This paradigm has arguably become the way that most of us think about the adaptation to pressure overload, has been refined with some modifications, such as indexation for height and other allometric measures,[9] and made its way into guideline documents.[4,10] One might add that the interest in the field of remodeling in pressure overload has experienced a renaissance with the introduction of transcutaneous aortic valve replacement and the ubiquity of elderly patients with moderate–to-severe or greater aortic stenosis.

However, as we have noted above and elsewhere,[11] not all pressure overload results in a concentric geometry of the LV: some patients with hypertension exhibit an eccentric remodeling pattern with normal systolic function[4,8]; others with aortic stenosis despite minimal LVH maintain normal LV systolic performance.[12] Furthermore in iPreserve, an important study of patients with heart failure with preserved ejection fraction (HFpEF), the prevalence of the concentric adaptations, concentric LVH and concentric remodeling accounted for little over half of the patients with HFpEF[13]; in other words, half of patients with HFpEF did not have concentric geometry.

These surprising findings have come at a time when we have a tool, CMR T1 mapping, which can noninvasively characterize the myocardial wall and help us better understand the relationship between form and function in hypertensive heart disease, and help us to understand why relatively modest LV remodeling is associated with heart failure and poor outcome. Native T1, which is the T1 of the myocardium in the absence of a contrast agent, is sensitive to the local microenvironment in both the intracellular and extracellular spaces.[14] As such, native T1 has a complex relationship to myocyte hypertrophy and interstitial space expansion because of myocardial fibrosis. By performing T1 mapping, both pre- and postcontrast administration, one can more specifically probe the fraction of myocardium which is extracellular, the extracellular volume (ECV), indirectly assessing myocardial fibrosis. The ECV reflects, on a voxel-wise basis, the relative fraction of extracellular space. Multiple studies have now analyzed changes in native T1 and ECV in hypertension and LVH.[15,16] Kuruvilla et al[15] were the first to demonstrate the increased native T1 and ECV in hypertensive heart disease patients with LVH. The study by Treibel et al[16] similarly showed increased ECV in patients with hypertensive LVH. Interestingly, neither study demonstrated increases in native T1 or ECV in patients with hypertension in the absence of LVH.

Kuruvilla et al[15] also demonstrated a correlation with regional systolic function (peak circumferential strain and

From the Departments of Medicine and Radiology, University of Massachusetts Medical School, Worcester (G.P.A.); and Departments of Medicine, Biomedical Engineering, Radiology and the Cardiovascular Imaging Center, University of Virginia Health System, Charlottesville (M.S.).

Correspondence to Gerard P. Aurigemma, MD, University of Massachusetts Medical School, Room ACC 4-238, 55 Lake Ave N, Worcester, MA 01655. E-mail gerard.aurigemma@umassmed.edu

(*Circ Cardiovasc Imaging*. 2017;10:e006975. DOI: 10.1161/CIRCIMAGING.117.006975.)

***Circ Cardiovasc Imaging* is available at http://circimaging.ahajournals.org**
DOI: 10.1161/CIRCIMAGING.117.006975

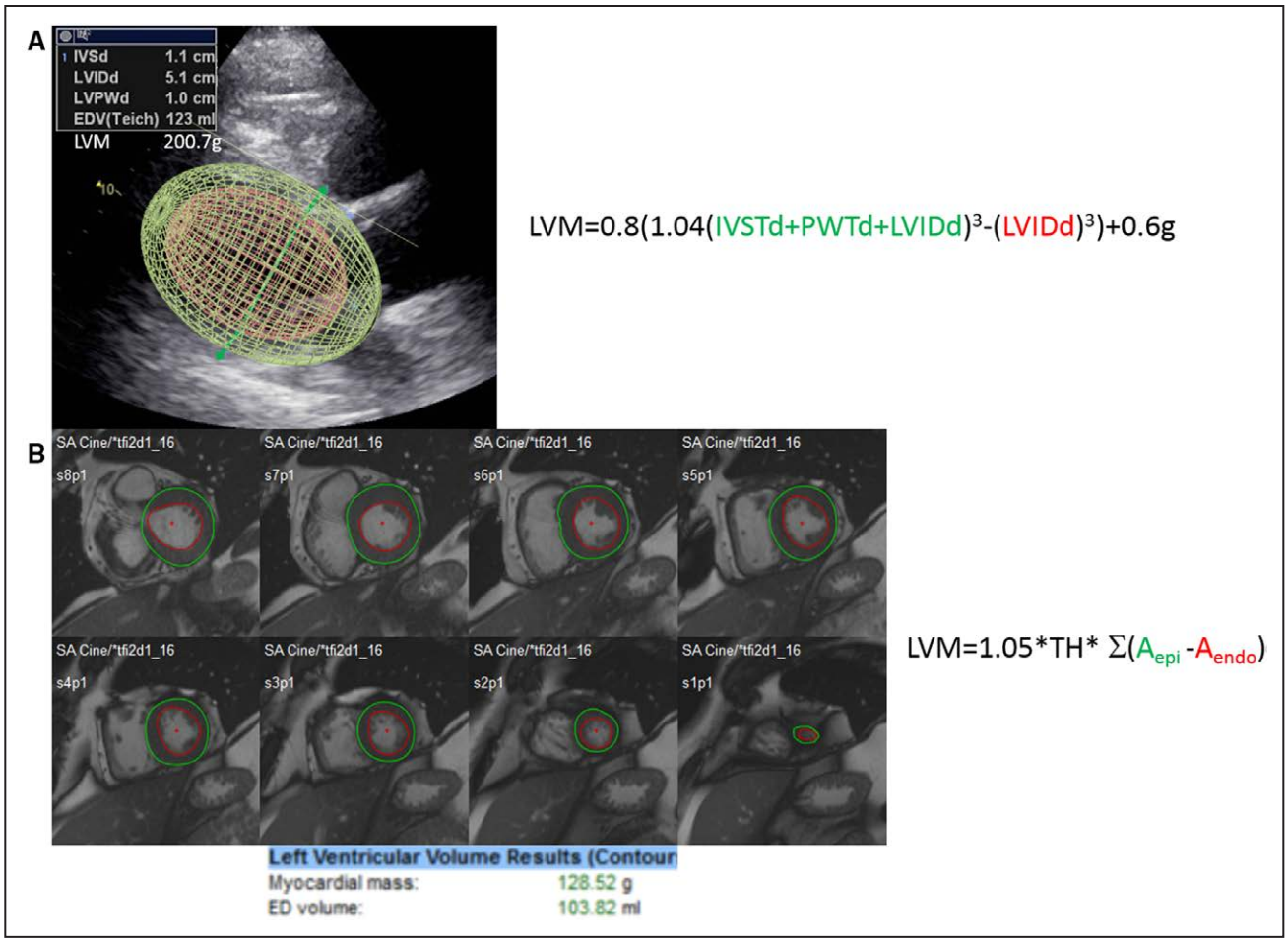

Figure. Composite figure showing the discrepancy between echo and cardiac magnetic resonance imaging (CMR) for the calculation of left ventricular (LV) mass in a representative patient. **A**, Two-shell model of the LV, assuming that the LV is a prolate ellipsoid of revolution; the echo cube method then computes 2 shells: the red shell indicating the inner LV cavity, drawn along the endocardial surface of the LV and the green shell representing the outer or epicardial shell of the LV. Subtracting the inner from outer shell yields the LV myocardial volume, which is then multiplied by specific gravity of myocardium to yield the LV mass. In this case, the LV dimensions specified yield an LV mass of 200.7 g. **B**, Method used to compute LV mass from series of 8 short-axis CMR images; the myocardial area is obtained similarly, by subtracting the inner from the outer shell and multiplying the sum by the specific gravity of myocardium. There is no need for a geometric assumption of LV shape, as with echocardiography. This calculation yields an LV mass of 128.5 g. LVM indicates left ventricular mass; IVSTd, septal thickness in diastole; PWTd, posterior wall thickness in diastole; LVIDd, left ventricular internal diameter in diastole.

early diastolic strain rate). This work extends observations made with CMR tagging and speckle-tracking strain imaging which has shown that some hypertensives with LVH and normal ejection fraction have abnormalities of regional function,[17,18] though such regional strain abnormalities are more likely to be observed with more severe hypertension.

With this background, we will review the CMR study by Goh et al[19] in the current issue of *Circulation: Cardiovascular Imaging*. This group presents a comprehensive study of LV remodeling among a large group of patients with treated hypertension, enrolled in a clinical trial, and assemble data not only on LV mass and geometry but also on the extent of fibrosis using CMR. They derive a novel descriptor—the remodeling index (RI)—and use it to gain insights into maladaptive remodeling among hypertensives. This parameter was derived by dividing the cube root of the LV cavity volume by the wall thickness, both measured at end diastole. The RI is therefore related to the inverse of RWT and to the mass/volume ratio. The authors conclude that low values of RI identify more CMR fibrosis and more LVH than standard parameters than these more established parameters of LV geometry.

Before we comment on the incremental value of the RI compared with RWT and mass/volume ratio, we should review some of the other findings of this work. First, there was only a weak association between blood pressure (either measured in the office or via ambulatory monitoring) and LV mass. Second, LV mass was positively associated with the extent of fibrosis. Third, most hypertensive patients did not have LVH, a finding that "echoes" the conclusions of Ganau et al.[8] Finally, those patients with LVH and low RI had higher LV mass index, more fibrosis, and higher values for the biomarkers studied. Interestingly, the group with the lowest RI tended to be younger and have a shorter duration of antihypertensive treatment.

What is new here? Those who follow the hypertensive heart disease literature will not be surprised to see that LV mass and blood pressure are positively but weakly correlated, even when ambulatory blood-pressure monitoring readings

are used; this finding has been known since the early days of echo-epidemiology.[20] This finding bespeaks the complicated relationship between the degree of pressure load and the adaptive response in humans, as opposed to experimental models, where the relationship between load and hypertrophy is much stronger.[21] The real question is the incremental value of the RI compared with RWT the mass/volume ratio. After all, the RWT and the mass/volume ratio are relatively easy to calculate, and both of these parameters have been in use for some time and normative values have been compiled over the years. The authors answer this question partially by showing that RI appears to provide the strongest correlation with fibrosis by CMR. Indeed, the data on RI and LV hypertrophy are interesting, particularly as the amount of interstitial fibrosis is inversely proportional to the RI, with the lowest values for RI associated with the most fibrosis, according to the authors. One might add that it would be interesting to know the various RI values at end systole, when myocardial load is much higher.

However, there are also some reasons to be cautious about adopting the RI. Those particularly interested in LV remodeling, in reading the fine print, will wonder why the investigators model the LV as a sphere. It is arguably just as easy to model the LV as a prolate ellipsoid using the formula V=4/3 (π)×a×b×c, where a, b, and c represent the 3 principal axes of the LV. Because the hypertensive LV is much more ellipsoid than it is spherical, this choice of geometric model is problematic. A simple gedanken experiment makes this point; if one uses a spreadsheet, models the LV as a sphere and then as a prolate ellipsoid, and varies LV dimension and wall thickness separately, it can be seen that increases in wall thickness decreases RI equally in a spherical as in prolate ellipsoid model; by contrast, chamber dilation increases the RI much less in a prolate ellipsoid model than in a spherical model. Thus, use of a spherical model might render the RI insensitive to the malefic effects of chamber dilation. Finally, if one were to consider percent changes in the more traditional parameter, the mass/volume ratio by the same type of exercise, it can be seen that the mass/volume ratio changes much more significantly when the LV geometry becomes much more concentric.

In their defense, though, the authors have shown that their RI better parallels fibrosis burden than does either the RWT or mass/volume ratio. This is a finding, which, if replicated, could support more widespread adoption of the RI. As far as the fibrosis data are concerned, a potential problem is that the authors quantify the total interstitial volume of the heart by multiplying the mean ECV by the LV mass. This product would presumably reflect the total amount of fibrosis in the heart rather than reflecting tissue-level interstitial fraction. They demonstrate an increased intracellular volume in patients with LVH by CMR. However, the authors do not provide data on ECV or native T1, which reflect local differences, and which should be somewhat independent of LV mass.

If we accept the authors' conclusions, one reason for the superiority of their RI compared with echocardiographic RWT or mass/volume ratio might be because of more reliable assessment of LV mass by CMR. This superiority is rooted in significant methodologic differences between echo and CMR. The most common echocardiographic method to measure LV mass is to use the ASE LVH equation as developed and validated by Devereux and Reichek.[22] This measurement is based on linear measurements of the anteroseptal and inferolateral wall, LV cavity at end diastole (Figure). The ASE equation takes the cube of these parameters, which based on a propagation of error analysis of the equation means that a 10% uncertainty in the measurement of the wall thickness (0.1 mm) results in a 10% error in LV mass which is on the order of 15 to 20 g, assuming a normal LV mass of 150 to 200 g. For CMR imaging, there are no geometric assumptions; the endocardial and epicardial borders are traced on 8 to 12 short-axis images and the myocardial volume is calculated using the Simpson method using the myocardial area on each image. A direct comparison between 2-dimensional echo and CMR demonstrated that CMR had a significantly lower uncertainty in assessment of LV mass (2.8%–4.8% versus 11.6%–15.7%; $P<0.001$).[23] Accordingly, the reduced uncertainty in the assessment of LV diastolic volume appears to be a strength of the RI in this article when compared with the uncertainty of cubing a LV cavity dimension.

Limitations notwithstanding, Goh et al[19] have provided interesting new data into the study of adaptation to pressure overload. Their conclusions are potentially applicable not only to hypertensive disease but to aortic stenosis and HFpEF: certainly, the expansion of the interstitial volume could have important diagnostic and prognostic implications for both of these increasingly encountered patients.[24] Although the data on HFpEF in this study are more hypothesis generating than conclusive, given the small numbers, the findings are plausible and interesting. Su et al[25] were the first to show that patients with HFpEF (who had increased LV mass) have increased ECV when compared with normal subjects and demonstrated a correlation between volumetric filling rates and ECV. In this study, the authors demonstrate increased total interstitial volume in patients with HFpEF and an increased RI in this group. However, the patients all had LVH, which is a component of the interstitial volume as defined in this study. Perhaps in future work, we will see the relationship between the RI and ECV or native T1.

Disclosures

None.

References

1. Gunther S, Grossman W. Determinants of ventricular function in pressure-overload hypertrophy in man. *Circulation*. 1979;59:679–688.
2. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med*. 1990;322:1561–1566. doi: 10.1056/NEJM199005313222203.
3. Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H; LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:995–1003. doi: 10.1016/S0140-6736(02)08089-3.
4. Marwick TH, Gillebert TC, Aurigemma G, Chirinos J, Derumeaux G, Galderisi M, Gottdiener J, Haluska B, Ofili E, Segers P, Senior R, Tapp RJ, Zamorano JL. Recommendations on the use of echocardiography in adult hypertension: a report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). *J Am Soc Echocardiogr*. 2015;28:727–754. doi: 10.1016/j.echo.2015.05.002.

5. Armstrong AC, Gidding S, Gjesdal O, Wu C, Bluemke DA, Lima JA. LV mass assessed by echocardiography and CMR, cardiovascular outcomes, and medical practice. *JACC Cardiovasc Imaging*. 2012;5:837–848. doi: 10.1016/j.jcmg.2012.06.003.
6. 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. *Eur Heart J Cardiovasc Imaging*. 2015;16:233–270. doi: 10.1093/ehjci/jev014.
7. Gaasch WH, Zile MR. Left ventricular structural remodeling in health and disease: with special emphasis on volume, mass, and geometry. *J Am Coll Cardiol*. 2011;58:1733–1740. doi: 10.1016/j.jacc.2011.07.022.
8. Ganau A, Devereux RB, Roman MJ, de Simone G, Pickering TG, Saba PS, Vargiu P, Simongini I, Laragh JH. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. *J Am Coll Cardiol*. 1992;19:1550–1558.
9. de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, Alderman MH. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. *J Am Coll Cardiol*. 1992;20:1251–1260.
10. 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;28:1–39.e14. doi: 10.1016/j.echo.2014.10.003.
11. Gaasch WH, Aurigemma GP. CMR imaging of extracellular volume and myocardial strain in hypertensive heart disease. *JACC Cardiovasc Imaging*. 2015;8:181–183. doi: 10.1016/j.jcmg.2014.12.002.
12. Kupari M, Turto H, Lommi J. Left ventricular hypertrophy in aortic valve stenosis: preventive or promotive of systolic dysfunction and heart failure? *Eur Heart J*. 2005;26:1790–1796. doi: 10.1093/eurheartj/ehi290.
13. Zile MR, Gottdiener JS, Hetzel SJ, McMurray JJ, Komajda M, McKelvie R, Baicu CF, Massie BM, Carson PE; I-PRESERVE Investigators. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. *Circulation*. 2011;124:2491–2501. doi: 10.1161/CIRCULATIONAHA.110.011031.
14. Taylor AJ, Salerno M, Dharmakumar R, Jerosch-Herold M. T1 mapping: basic techniques and clinical applications. *JACC Cardiovasc Imaging*. 2016;9:67–81. doi: 10.1016/j.jcmg.2015.11.005.
15. Kuruvilla S, Janardhanan R, Antkowiak P, Keeley EC, Adenaw N, Brooks J, Epstein FH, Kramer CM, Salerno M. Increased extracellular volume and altered mechanics are associated with LVH in hypertensive heart disease, not hypertension alone. *JACC Cardiovasc Imaging*. 2015;8:172–180. doi: 10.1016/j.jcmg.2014.09.020.
16. Treibel TA, Zemrak F, Sado DM, Banypersad SM, White SK, Maestrini V, Barison A, Patel V, Herrey AS, Davies C, Caulfield MJ, Petersen SE, Moon JC. Extracellular volume quantification in isolated hypertension - changes at the detectable limits? *J Cardiovasc Magn Reson*. 2015;17:74. doi: 10.1186/s12968-015-0176-3.
17. Narayanan A, Aurigemma GP, Chinali M, Hill JC, Meyer TE, Tighe DA. Cardiac mechanics in mild hypertensive heart disease: a speckle-strain imaging study. *Circ Cardiovasc Imaging*. 2009;2:382–390. doi: 10.1161/CIRCIMAGING.108.811620.
18. Palmon LC, Reichek N, Yeon SB, Clark NR, Brownson D, Hoffman E, Axel L. Intramural myocardial shortening in hypertensive left ventricular hypertrophy with normal pump function. *Circulation*. 1994;89:122–131.
19. Goh VJ, Le T-T, Bryant J, Wong JI, Su B, Lee C-H, Pua E, Sim CPY, Ang B, Choon Aw T, Cook SA, Chin CWL. Novel index of maladaptive myocardial remodeling in hypertension. *Circ Cardiovasc Imaging*. 2017;10:e006840. doi: 10.1161/CIRCIMAGING.117.006840.
20. Bhatt DL, James GD, Pickering TG, Devereux RB. Relation of arterial pressure level and variability to left ventricular geometry in normotensive and hypertensive adults. *Blood Press Monit*. 1996;1:415–424.
21. Norton GR, Woodiwiss AJ, Gaasch WH, Mela T, Chung ES, Aurigemma GP, Meyer TE. Heart failure in pressure overload hypertrophy. The relative roles of ventricular remodeling and myocardial dysfunction. *J Am Coll Cardiol*. 2002;39:664–671.
22. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation*. 1977;55:613–618.
23. Grothues F, Smith GC, Moon JC, Bellenger NG, Collins P, Klein HU, Pennell DJ. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol*. 2002;90:29–34.
24. Salerno M. Seeing the unseen fibrosis in heart failure with preserved ejection fraction. *JACC Cardiovasc Imaging*. 2014;7:998–1000. doi: 10.1016/j.jcmg.2014.05.012.
25. Su MY, Lin LY, Tseng YH, Chang CC, Wu CK, Lin JL, Tseng WY. CMR-verified diffuse myocardial fibrosis is associated with diastolic dysfunction in HFpEF. *JACC Cardiovasc Imaging*. 2014;7:991–997. doi: 10.1016/j.jcmg.2014.04.022.

KEY WORDS: Editorials ■ echocardiography ■ hypertension ■ hypertrophy ■ magnetic resonance imaging

Circulation
Cardiovascular Imaging

A Novel Index of Remodeling in Hypertensive Heart Disease

Gerard P. Aurigemma and Michael Salerno

Circ Cardiovasc Imaging. 2017;10:
doi: 10.1161/CIRCIMAGING.117.006975
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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