REVIEW ARTICLE

Left Ventricular Hypertrophy: The Relationship between the Electrocardiogram and Cardiovascular Magnetic Resonance Imaging

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Conventional assessment of left ventricular hypertrophy (LVH) using the electrocardiogram (ECG), for example, by the Sokolow–Lyon, Romhilt–Estes or Cornell criteria, have relied on assessing changes in the amplitude and/or duration of the QRS complex of the ECG to quantify LV mass. ECG measures of LV mass have typically been validated by imaging with echocardiography or cardiovascular magnetic resonance imaging (CMR). However, LVH can be the result of diverse etiologies, and LVH is also characterized by pathological changes in myocardial tissue characteristics on the genetic, molecular, cellular, and tissue level beyond a pure increase in the number of otherwise normal cardiomyocytes. For example, slowed conduction velocity through the myocardium, which can be due to diffuse myocardial fibrosis, has been shown to be an important determinant of conventional ECG LVH criteria regardless of LV mass. Myocardial tissue characterization by CMR has emerged to not only quantify LV mass, but also detect and quantify the extent and severity of focal or diffuse myocardial fibrosis, edema, inflammation, myocarditis, fatty replacement, myocardial disarray, and myocardial deposition of amyloid proteins (amyloidosis), glycolipids (Fabry disease), or iron (siderosis). This can be undertaken using CMR techniques including late gadolinium enhancement (LGE), T1 mapping, T2 mapping, T2* mapping, extracellular volume fraction (ECV) mapping, fat/water-weighted imaging, and diffusion tensor CMR. This review presents an overview of current and emerging concepts regarding the diagnostic possibilities of both ECG and CMR for LVH in an attempt to narrow gaps in our knowledge regarding the ECG diagnosis of LVH.

Ann Noninvasive Electrocardiol 2014;19(6):524–533

noninvasive techniques; electrocardiography; cardiac MRI

The diagnosis of left ventricular hypertrophy (LVH) in clinical practice is a finding that requires the attention of the clinician. It has been documented that LVH detected by echocardiography or the electrocardiogram (ECG) is a risk factor for cardiac morbidity or mortality which is independent of other known risk factors including blood pressure and left ventricular mass.[1–3]

In hypertensive patients, the finding of LVH in a patient has a direct impact on therapy. LVH detected by both echocardiography and ECG define target organ damage, and according to the European Society of Cardiology guidelines[4] the presence of target organ damage is a key factor in the management of the hypertensive patient.

It has also been shown that antihypertensive therapy decreases signs of LVH by echocardiography or ECG that are associated with improvement of the clinical status and prognosis of a hypertensive patient,[5–7] and thus the benefit of antihypertensive therapy can be monitored. However, these straightforward statements lead to a number of unanswered questions.

It has repeatedly been documented that the diagnostic performance of the ECG for LVH detection is not satisfactory considering the low sensitivity

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DOI:10.1111/anec.12223

and varying specificity.[8] Furthermore, there are 37 different ECG LVH criteria recommended by the American Heart Association, thus making the status of ECG criteria for LVH a potential source of confusion for the clinician.

The variability of the ECG LVH criteria has in part been attributed to the imprecision of echocardiography as a reference method for estimating left ventricular (LV) mass. Subsequently, cardiovascular magnetic resonance imaging (CMR) has been shown to be a far more precise method for determining LV mass compared to echocardiography.[10] Importantly, CMR provides additional possibilities for assessment of myocardial tissue characteristics of relevance for LVH beyond measurement of LV mass alone.

In this review, the diagnostic possibilities of both ECG and CMR for LVH are discussed in an attempt to narrow gaps in our knowledge regarding the ECG diagnosis of LVH. Bridging these gaps is vital in order to elucidate the information necessary to inform clinical management of individual patients.

LEFT VENTRICULAR HYPERTROPHY

LVH is defined as an increased LV mass. However, the increase in LV mass is not the only attribute that is changed in LVH.

A more comprehensive definition of hypertrophy defines hypertrophy as an increase in size of the tissue due to an increase in size of the cells in that tissue without increasing their number, thus differentiating hypertrophy from hyperplasia. Consequently, LVH necessitates that the increase in LV mass is due to the increase in size, not number, of the cardiomyocytes comprising the LV. However, the hypertrophic myocardium also undergoes more complex changes affecting both the cardiomyocytes and the interstitium. These changes may include focal or diffuse fibrosis, inflammation, edema, fatty infiltration, ischemic cellular changes due to the imbalance between increased LV mass and blood supply, or abnormal myocardial deposition of substances, including but not limited to amyloid protein (amyloidosis), glycolipids (Fabry disease), and iron (siderosis). Notably, an additional factor to be considered is the time course of development and progress of the hypertrophic process.[11,12] Furthermore, the increase in mass can differ at the tissue, cellular, subcellular, molecular, and genetic levels. These conditions influence the electrophysiological impulse generation and propagation through the ventricles, and consequently impact the resultant ECG.

ELECTROCARDIOGRAPHY

The ECG records the manifestation of electrical activity of the heart as measured on the body surface. The cardiac electric field generated by the heart depends on both active and passive electrical properties of the heart and torso on the electrical impulse generation and propagation through the myocardium. For the sake of simplicity, the electrical properties of the torso will be not reviewed in further detail here.

LVH is a process of complex rebuilding and remodeling of the LV myocardium, including electrophysiological remodeling. The diagnostic accuracy of the ECG LVH criteria have been evaluated in relation to a reference method, such as echocardiography or CMR, which best estimates the major characteristic of LVH—the increase in LV mass. Evaluation of the accuracy and precision of the ECG criteria for estimating LV mass implies that the ECG is a surrogate method for estimating LV mass. However, this view of the ECG as a method for estimating LV mass is unfortunate considering that the generated electric field in general, and the cardiac electric field in particular, does not depend exclusively on the amount of LV myocardium.

CONVENTIONAL ECG CONCEPTS IN LVH

The principal ECG-derived diagnostic characteristics for LVH detection include an increased QRS complex amplitude, an increased QRS complex duration, a leftward shift of electrical axis of the QRS in frontal plane, and ST-segment deviation and T wave changes associated with left ventricular strain.[9] Furthermore, more advanced ECG methods based on combined multivariate statistics of measures from the ECG have shown promise in diagnosing LVH.[13] In addition to conventional 12-lead ECG measures of QRS amplitudes and durations, those statistical approaches incorporated measures including, among others, the spatial QRS–T angle from the 12-lead ECG transformed

into a vectorcardiogram, high-frequency ECG components of the QRS complex, and heart rate variability from 5-minute long ECG recordings at rest.[13] The role of these advanced statistical measures for helping to better understand LVH remains to be explored.

The increased QRS complex amplitude is attributed to the increased extent of the electrical activation front passing through the enlarged LV. The enlarged LV also creates a longer trajectory for the activation front to pass, that is, a longer time required, and sometimes also a slowed conduction velocity through the hypertrophied myocardium. Taken together, these changes contribute to a prolonged QRS complex duration.

CMR in Understanding the ECG in LVH

The ECG LVH criteria were developed using comparative studies which directly or indirectly estimated LV size or mass. The morphology and duration of the QRS complex have been attributed to the globally increased LV mass and/or considerations of the LV wall thickness and LV diameter (concentric or eccentric remodeling and/or dilation). By comparison, CMR provides three-dimensional coverage of the LV without image quality limitations related to ultrasound transmission, and is thus more accurate in estimating dimensions of the LV compared to echocardiography. Furthermore, CMR can be used to evaluate the three dimensional geometry of the extent of hypertrophy, which can be considerably asymmetric in the setting of hypertrophic cardiomyopathy.[14] Taken together, CMR provides highly accurate, precise and reproducible estimates of LV anatomy and mass, and is the in vivo reference standard for measuring LV mass.[15–18] The increased precision has made CMR the preferred method for clinical trials where LV mass is an endpoint. For example, a study seeking to detect a 10-g reduction in LV mass following a therapeutic intervention with 90% power and $P < 0.05$ would require a sample size of $n = 273$ by echocardiography, but only $n = 9$ by CMR.[10]

However, even considering the advantages of CMR estimates of LV mass over echocardiography, the discrepancies between ECG LVH criteria and LV mass persist. The correlation coefficients between LV mass index and ECG LVH indices have recently been reported to range between $r = -0.02$ ($P = 0.94$) for the Sokolow–Lyon index in women to $r = 0.76$ ($P < 0.001$) for the Cornell voltage criteria in men.[19]

Since the hypertrophied myocardium is pathologically altered in more ways than just increase mass, it is apparent that ECG LVH has to move beyond estimation of LV mass.[20] With regards to the physiological basis for generating the ECG, it has been documented that the conduction velocity in the hypertrophied LV myocardium is slower than normal.[21–23] The slowing in conduction velocity is understood to be a determinant of QRS duration prolongation. However, diffuse or regionally slowed conduction velocity in the LV also changes the shape of the activation front and consequently the magnitude and orientation of the depolarization vectors.

Simulation studies have shown that LV mass is not the main and only determinant of QRS voltage.[24,25] In these simulations, QRS amplitude and duration were not proportional to the increase in LV mass. Rather, considerable changes resulted from conduction velocity slowing in the LV, even in the normal sized heart. Slowing the conduction velocity in the LV in combination with anatomical changes in the LV resulted in a spectrum of QRS patterns that have been documented in patients with LVH. These include increased QRS voltage, prolonged QRS duration, left axis deviation, prolonged intrinsicoid deflection (the time from QRS onset to the peak of the R wave), as well as a QRS pattern typical of left bundle branch block. Moreover, slowed conduction velocity has been shown to increase the values of clinically used ECG-LVH criteria. Specifically, such is the case when applied to the Sokolow–Lyon index and the Cornell criteria in all simulated anatomical types of LVH as well as in the normal sized heart. Interestingly, the Cornell voltage-duration product, which is recommended as a sensitive ECG marker of increased LV mass showed negligible association with the increase in LV mass and/or type of hypertrophy. On the contrary, it was slowed conduction velocity that resulted in an increase in Cornell voltage-duration product in the reference heart as well as in all simulated anatomical types of LVH. These simulation results indicate that the clinical ECG-LVH criteria, especially the Cornell voltage-duration product, more so reflect changes in the electrical properties of the hypertrophied myocardium than an increase in LV mass per se.

Furthermore, regional slowing of conduction velocity in the LV has been shown to lead to

changes in the QRS amplitude and morphology consistent with ECG LVH criteria. A slower conduction velocity in the anteroseptal region of the LV resulted in QRS complex changes that are analogous to diagnostic ECG LVH criteria or QRS patterns frequently seen in patients with LVH; namely an increase in R_I, S_{III}, and aVL amplitudes, that is, in leads that create basis for the limb lead QRS voltage criteria.[26–28] The increased R wave in aVL is a component of both the Cornell voltage criteria[29] and the Cornell voltage-duration product.[30] Slowing in the anteroseptal region affected four of six components of the Romhilt–Estes score[31]: R and S amplitude in limb leads, left axis deviation, prolongation of the QRS complex, and intrinsicoid deflection prolongation. Theoretically, slowed conduction could account for a total of seven points in the Romhilt–Estes score, thus exceeding the cutoff value of five points for defining LVH. Additionally, the shift of electrical axis to the left and the presence of a small Q wave in aVL results in a QRS pattern of left anterior fascicular block, which is an ECG finding frequently seen in patients with LVH.

Taken together, both diffuse and focally slowed conduction velocities in the LV myocardium resulted either in an increased QRS voltage or in QRS patterns consistent with ECG findings in LVH, despite an unchanged LV size or mass.

CMR Assessment of LVH Beyond LV Mass

In clinical practice, direct in vivo measurement of conduction velocity is not possible. However, CMR can be used to detect and characterize a number of myocardial pathologies which may affect conduction velocity to varying extents. Such myocardial pathologies detectable by CMR include focal scarring of either ischemic or non-ischemic origin,[32–34] diffuse fibrosis,[35] edema,[36,37] inflammation,[38] fatty infiltration,[39] or abnormal myocardial deposition of substances such as amyloid protein,[40–42] glycolipids,[43] and iron.[44,45] As mentioned above, the increased mass in LVH is not solely the result of an increased amount of normal tissue. In less common cases, hypertrophy may be related to abnormal myocardial deposition of glycolipids, iron or amyloid, which also may affect ECG. Specifically, glycolipid overload as seen in Fabry disease is associated both with LVH and ECG changes mostly in the P-wave duration,[46] whereas some types of iron overload patients are more likely to develop hypertension and LVH,[47] and subsequent LVH-related ECG repolarization changes,[48] and amyloid leads to reduced QRS amplitudes in general.[41] More commonly, the hypertrophied myocardium may exhibit increased strain either in the absence or presence of focal scarring, may have genetic etiologies, and may include hypertrophied cardiomyocytes which undergo changes that can affect the ECG, including abnormal arrangement of cardiomyocytes, an increase in fibrous tissue and cell atrophy.[49,50] Additionally, the cardiomyocytes can suffer from ischemia which is an additional factor affecting the ECG and the structure of myocardial tissue. There may also be inflammatory components and adipose tissue, either as a part of the hypertrophic process or related to comorbidities.[51–53]

Detection of Focal and Diffuse Fibrosis by CMR

Hypertrophy is accompanied by an increase in connective tissue that has been documented by histopathological studies both in animal experiments and clinical studies.[54,55] In terms of affecting the ECG, fibrosis affects the impulse propagation at least in two ways. First, the proportion of electrically active to inactive tissue decreases. Second, the activation front is fractioned and the impulse propagation slowed. Focal fibrotic tissue can be considered as electrically inactive and nonconductive tissue, although a possible electrical connection between cardiomyocytes and fibroblasts has been described.[56,57]

CMR can be used to detect and quantify both the extent and severity of both diffuse fibrosis and focal fibrosis. It is important to emphasize the difference between focal and diffuse fibrosis. CMR can be used to quantitatively characterize both focal and diffuse fibrosis by measuring the percent of myocardium comprised of extracellular space. The method is called extracellular volume fraction (ECV) CMR, and normal myocardium has an ECV of 20%–30%.[33,58] Focal fibrosis, also referred to as scar, typically forms following myocardial infarction or scarring of other nonischemic etiologies such as myocarditis, but also LVH of various origins, among others. Focal fibrosis is characterized by a high severity loss of cardiomyocytes where by ECV can measure up toward 50%–90% of the tissue by volume,

and is comprised of replacement tissue including fibroblasts and collagen which develop in the chronic healing phase following an episode of necrosis of ischemic or nonischemic origin.[33,59]

Detection of focal fibrosis in individuals with LVH is important considering the cardiac complications associated with focal fibrosis. Such complications include ventricular dysfunction, reduced coronary flow reserve, ventricular arrhythmias, and adverse prognosis.[60–62] Moreover, these factors are also likely to affect the potential for regression of LVH following antihypertensive therapy or valvular surgery. Notably, little interest has been devoted to the analysis of QRS complex patterns in relation to the location and extent of fibrosis, or other electrically inactive tissue, in relation to the presence or potential for regression of LVH.

By comparison, diffuse fibrosis is a global low severity reactive phenomenon typically caused by hypertension, increased strain due to valvular disease, strain remote from focal scarring, age, diabetes, or other causes. In diffuse fibrosis, ECV can typically measure 30%–40%, and is composed of an increased amount of collagen in the interstitium of cardiomyocytes of normal quantity.[33,59] While ECV-CMR is a relatively new technique for quantifying both the extent and severity of focal and diffuse fibrosis, CMR has traditionally been used to quantify the extent of focal fibrosis with the late gadolinium enhancement (LGE) technique. Focal fibrosis detected by LGE-CMR is a frequent feature of LVH, regardless of its cause.[39,40] By comparison, diffuse fibrosis can only be detected by techniques such as ECV-CMR and related techniques including postcontrast T1 mapping.[63] An increase in myocardial ECV consistent with diffuse fibrosis has been found in such pathologies as aortic stenosis,[64] dilated cardiomyopathy,[65] adolescent obesity,[66] LVH due to sarcomere mutations,[67] and with increasingage.[33] Furthermore, ECV-CMR and related techniques have a potential to identify unexpected diffuse fibrosis in a significant proportion of athletes and veteran athletes.[68] Finally, the combination of LGE- and ECV-CMR provides a unique noninvasive evaluation of patterns of both focal and diffuse fibrosis in LVH. Detection of both focal and diffuse myocardial fibrosis is of utmost diagnostic importance since it is a marker of severity of LVH and a potential arrhythmogenic mechanism,[69–72] as well as a prognostic marker of mortality.[73]

The Use of CMR for Myocardial Tissue Characterization Beyond Fibrosis

LGE- and ECV-CMR are, however, not specific for fibrosis. These techniques may identify any pathology which increases the myocardial extracellular space. While fibrosis increases ECV, other pathologies may also increase ECV, including edema or inflammation,[36,38] necrosis,[37] as well as myocardial amyloid deposition.[40–42] Importantly, diffusely increased ECV has been shown to provide incremental prognostic value for survival beyond ejection fraction.[74] However, these conditions can be differentiated from focal and diffuse fibrosis because focal and diffuse fibrosis exhibit little or no increase in myocardial T1 in the absence of contrast administration, also called native T1. Furthermore, diffusely reduced myocardial native T1 is a specific finding for myocardial iron or glycolipid (Fabry) overload disease, both of which may exhibit LVH. Also, both T1 mapping and other techniques for fat imaging by CMR[39] can identify focal fatty infiltration. An additional myocardial tissue characteristic of interest in LVH is myocardial disarray. Myocardial disarray can be evaluated by cardiac diffusion tensor imaging by CMR (DT-CMR), and proof-of-concept and measurement variability studies have been performed in both healthy volunteers[75] and patients with hypertrophic cardiomyopathy.[76] Importantly, CMR can identify these alternative etiologies for, or related to, LVH in order to better understand the relationship between ECG findings and LVH-related myocardial pathologies. See Table 1 for a summary of the myocardial characteristics detectable by CMR which affect the ability of the ECG to quantitatively assess LVH.

REGRESSION OF LVH BY ECG AND CMR

A topic related to diagnosing LVH is the ability to detect regression of LVH. Regression of LVH defined as reduction in LV mass is a topic with conflicting findings regarding the improved outcomes during pharmacological treatment for hypertension. On the one hand, an improved prognosis has been reported,[52–54] and on the other hand, negative results have been reported.[55,56] CMR has been used to show that the reduction in LV mass following surgical treatment for aortic

Table 1. Myocardial Characteristics Detectable by Cardiovascular Magnetic Resonance Imaging (CMR) that Affect the Ability of the Electrocardiogram to Quantitatively Assess Left Ventricular Hypertrophy

Pathophysiological Characteristic	CMR Technique
Left/right ventricular volumes and mass	Volumetric measurement in cine images
Regional myocardialwallthickness	3D distribution in cine images
Focal myocardial fibrosis (scar)	Late gadolinium enhancement
Diffuse myocardial fibrosis in the absence of scar	ECV mapping
Diffuse myocardial edema/inflammation	T1 mapping, T2 mapping
Focal myocardial edema/inflammation	T1 mapping, T2 mapping, T2-weighted imaging
Focal myocardial fatty replacement	T1 mapping, Fat/water-weighted imaging
Diffuse myocardial amyloid deposition	ECV mapping, T1 mapping
Diffuse myocardial glycolipid deposition (Fabry)	T1 mapping
Diffuse myocardial iron overload (siderosis)	T1 mapping, T2* measurement
Myocardial disarray	Diffusion Tensor CMR

CMR = cardiovascular magnetic resonance imaging; ECV = extracellular volume; 3D = three-dimensional. See text for further details on the respective techniques.

stenosis is related to reduction in myocardial cell size, with no reduction in the amount of diffuse fibrosis (extracellular collagen) detected by ECV-CMR.[77] The combination of CMR and ECG thus shows potential as a tool for elucidating how these changes are manifested in the ECG.

Taking together, CMR and ECG provide complementary information about the size and tissue characteristics of the myocardium, and could be used in combination to shape a new view of the agreements and discrepancies between the two methods in order to potentially move the assessment of LVH by ECG beyond the current estimation of LV mass.

FUTURE PERSPECTIVES

Even when taking into account the current state-of-the-art CMR methods for myocardial tissue characterization in humans, there remain additional tissue characteristics of relevance for the ECG that currently cannot be elucidated by CMR. CMR cannot currently provide information on the electrical impulse generation of the action potential, electrical impulse propagation through the hypertrophied cardiomyocytes, the alterations in the architecture of intercellular connection components and micro-heterogeneity. Of note, CMR has been used in animal models to noninvasively measure the absolute size of cardiomyocytes by assessment of the intracellular lifetime of water (τ_{ic}). This CMR method is based on assessment the dynamics of a conventional clinical gadolinium-based CMR contrast agent.[78] While translation of this technique to humans remains to be undertaken, the technique shows promise considering that it has been validated histologically, and has been able to noninvasively detect and quantify increased myocardial cell size in a murine model of LVH.[78]

Although the main changes in the action potential of hypertrophied cardiomyocytes are observed during the repolarization phase, the ion channels involved in depolarization (the fast sodium current INa, L-type calcium current ICa(L) and Na^+–Ca^{2+} exchanger INa/Ca) are also affected, and further modified by a broad spectrum of changes observed in LVH. Such changes include variations in ion concentration (e.g., Na^+, Ca^{2+}), gene expression, metabolic changes, energy metabolism, and many others.[89–86] While there exist theoretical possibilities to interrogate the role of sodium in the heart by ^{23}Na-CMR in relation to ECG findings,[92] such capabilities have neither been explored nor are currently readily clinically available.

The velocity of electrical impulse propagation in a single hypertrophied cardiomyocyte has been shown to be increased. On the one hand, this is in accordance with cable theory, since the increase in diameter of the cardiomyocyte (analogously to the cable) leads to a decrease in the resistance and increase in conductivity.[88,89] On the other hand, however, the intercellular coupling in hypertrophy is remarkably altered leading to slowed conduction velocity. The alterations include connexin43 (Cx43) expression and intracellular coupling reduction,

and gap junction channels redistribution.[90–94] The observed slowing of conduction velocity results in decrease in QRS amplitude and changes in QRS pattern, as documented in experimental and simulation studies.[95–97]

The nonuniform changes on the microscopic scale, such as in size of hypertrophied cardiomyocytes,[98,99] Cx43 reduction, gap junction location,[100,102] action potential morphology and membrane currents characteristics[103,104] create microscopic heterogeneity. Together, these factors result in alteration of the normal ordered pattern of the microconduction pathway in LVH even when the activation front is not deformed. Whether or not these microscopic factors can be interrogated noninvasively in humans using CMR or other methods to better understand the ECG in LVH certainly constitute challenges to the field.

CONCLUSION

CMR provides a number of robust noninvasive techniques offering a spectrum of specific approaches for noninvasive in vivo characterization of pathological processes in the myocardium that could expand our understanding of ECG changes in LVH. The analysis of both agreement and discrepancies between ECG and CMR may provide information that can contribute to understanding the wide spectrum of ECG changes seen in LVH, and their diagnostic and prognostic importance. Using CMR and ECG as complementary methods will also open new questions based on understanding the diagnostic power of both methods—a space where we have to direct the future research to approach the LVH diagnostic problem systematically. While CMR has developed to be able to identify a number pathological processes in the myocardium, the characterization of LVH, in particular on the microscopic scale, is still lacking. While the agreement between CMR and ECG for characterizing LVH will likely remain far from perfect owing to the fundamental biophysical differences between the underlying technical principles of the techniques, improvements in the understanding of LVH have been made using CMR and ECG, and the new and emerging CMR and ECG techniques hold promise for continued improvements.

REFERENCES

1. Levy D, Anderson KM, Savage DD. Echocardiographically detected left ventricular hypertrophy: Prevalence and risk factors: The Framingham. Heart Study Ann Intern Med 1988;108(1):7–13.
2. Kannel WB, Gordon T, Castelli WP, et al. Electrocardiographic left ventricular hypertrophy and risk of coronary heart disease: The Framingham study. Ann Intern Med 1970;72:813–822.
3. Sundström J, Lind L, Arnlöv J, et al. Echocardiographic and electrocardiographic diagnoses of left ventricular hypertrophy predict mortality independently of each other in a population of elderly men. Circulation 2001;103:2346–2351.
4. Mancia G, Fagard R, Narkiewicz K, et al. Task Force Members: 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013;31:1281–1357.
5. Curry CL, Robinson H, Brown R, et al. Regression of left ventricular hypertrophy in patients with essential hypertension. Results of 6 month treatment with indapamide. Am J Hypertens 1996;9:828–832.
6. Sheridan DJ. Left ventricular hypertrophy regression: The LIVE trial. Cardiologia 1999;44(Suppl 1):541–543.
7. Okin PM, Devereux RB, Jern S, et al. Regression of electrocardiographic left ventricular hypertrophy by losartan versus atenolol: The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study. Circulation 2003;108:684–690.
8. Pewsner D, Jüni P, Egger M, et al. Accuracy of electrocardiography in diagnosis of left ventricular hypertrophy in arterial hypertension: Systematic review. BMJ 2007;335(7622):711–719.
9. Hancock EW, Deal BJ, Mirvis DM, et al. AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram. Part V: Electrocardiogram Changes Associated With Cardiac Chamber Hypertrophy A Scientific Statement From the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. J Am Coll Cardiol 2009;53:992–1002.
10. Bellenger NG, Davies LC, Francis JM, et al. Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2000;2(4):271–278.
11. Meerson FZ. The myocardium in hyperfunction, hypertrophy and heart failure. Circ Res 1969;25(Suppl. II):II-1–II-163.
12. Fizel A, Fizelova A, Turcany M. The relations between ultrastructural and metabolic changes of the myocardium of the hypertrophied and failing heart [Vztah medziultrastrukturalnymi a metabolickymi zmenami myokardu hypertrofovaneho a zlyhavajuceho srdca]. Folia Fac Med Uni vComeniane Bratisl 1984;22:9–119 (in Slovak, abstract in English).
13. Schlegel TT, Kulecz WB, Feiveson AH, et al. Accuracy of advanced versus strictly conventional 12-lead ECG for detection and screening of coronary artery disease, left ventricular hypertrophy and left ventricular systolic dysfunction. BMC Cardiovasc Disord 2010;10:28.
14. Florian A, Masci PG, De Buck S, et al. Geometric assessment of asymmetric septal hypertrophic cardiomyopathy by CMR. J Am Coll Cardiol 2012;5:702–711.

15. Pennell DJ, Sechtem UP, Higgins CB, et al. Clinical indications for cardiovascular magnetic resonance (CMR): Consensus Panel report. Eur Hear J 2004;25:1940–1965.
16. Stephensen SS, Carlsson M, Ugander M, et al. Agreement of left ventricular mass in steady state free precession and delayed enhancement MR images: Implications for quantification of fibrosis in congenital and ischemic heart disease. BMC Med Imaging 2010;10:4–10.
17. Katz J, Milliken MC, Stray-Gundersen J, et al. Estimation of human myocardial mass with MR imaging. Radiology 1988;169:495–498.
18. Lorenz CH, Walker ES, Morgan VL, et al. Normal human right and left ventricular mass, systolic function, and gender differences by cine magnetic resonance imaging. J Cardiovasc Magn Reson 1999;1:7–21.
19. Courand PY, Gaudebout N, Mouly-Bertin C, et al. Biological, electrical and echocardiographic indices versus cardiac magnetic resonance imaging in diagnosing left ventricular hypertrophy. Hypertens Res 2014;37:444–451.
20. Bacharova L, Estes EH, Bang LE, et al. Second statement of the Working Group on Electrocardiographic Diagnosis of Left Ventricular Hypertrophy. J Electrocardiol 2011;44:568–570.
21. McIntyre H, Fry CH. Abnormal action potential conduction in isolated human hypertrophied left ventricular myocardium. J Cardiovasc Electrophysiol 1997;8:887–894.
22. Cooklin M, Wallis WR, Sheridan DJ, et al. Conduction velocity and gap junction resistence in hypertrophied, hypoxic quinea-pig left ventricular myocardium. Exp Physiol. 1998;83:763–770.
23. Lai YJ, Chen YY, Cheng CP, et al. Changes in ionic currents and reduced conduction velocity in hypertrophied ventricular myocardium of Xin α-deficient mice. Anatolian J Cardiol 2007;7(Suppl 1):90–92.
24. Bacharova L, Szathmary V, Kovalcik M, et al. Effect of changes in left ventricular anatomy and conduction velocity on the QRS voltage and morphology in left ventricular hypertrophy: A model study. J Electrocardiol 2010;43:200–208.
25. Bacharova L, Szathmary V, Mateasik A. QRS complex and ST segment manifestations of ventricular ischemia: The effect of regional slowing of ventricular activation. J Electrocardiol 2013;46:497–504.
26. Lewis T. Observations upon ventricular hypertrophy with special reference to preponderance of one or the other chamber. Heart 1914;5:367–402.
27. Gubner RS, Ungerlieder HE. Electrocardiographic criteria of left ventricular hypertrophy: Factors determining the evolution of the electrocardiographic patterns in hypertrophy and bundle branch block. Arch Intern Med 1943;72:196–209.
28. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar and limb leads. Am Heart J 1949;37:161–186.
29. Casale PN, Devereux RB, Alonso DR, et al. Improved sex-specific criteria of left ventricular hypertrophy for clinical and computer interpretation of electrocardiograms: Validation with autopsy findings. Circulation 1987;75:565–572.
30. Molloy TJ, Okin PM, Devereux RB, et al. Electrocardiographic detection of left ventricular hypertrophy by the simple QRS voltage-duration product. J Am Coll Cardiol 1992;20:1180–1186.
31. Romhilt DW, Estes EH Jr. A point score system for the ECG diagnosis of left ventricular hypertrophy. Am Heart J 1968;75:752–758.
32. Kim RJ, Fieno DS, Parrish TB, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation 1999;100:1992–2002.
33. Ugander M, Oki AJ, Hsu LY, et al. Extracellular volume imaging by magnetic resonance imaging provides insights into overt and sub-clinical myocardial pathology. Eur Heart J 2012;33:1268–1278.
34. Mahrholdt H, Wagner A, Judd RM, et al. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. Eur Heart J 2005;26:1461–1474.
35. Flett AS, Hayward MP, Ashworth MT, et al. Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis: Preliminary validation in humans. Circulation 2010;122:138–144.
36. Ugander M, Bagi PS, Oki AJ, et al. Myocardial edema as detected by pre-contrast T1 and T2 CMR delineates area at risk associated with acute myocardial infarction. J Am Coll Cardiol 2012;5:596–603.
37. Dall'Armellina E, Ferreira VM, Kharbanda RK, et al. Diagnostic value of pre-contrast T1 mapping in acute and chronic myocardial infarction. J Am Coll Cardiol 2013;6:739–742
38. Ferreira VM, Piechnik SK, Dall'Armellina E, et al. T(1) mapping for the diagnosis of acute myocarditis using CMR: Comparison to T2-weighted and late gadolinium enhanced imaging. J Am Coll Cardiol 2013;6:1048–1058.
39. Kellman P, Hernando D, Arai AE. Myocardial Fat Imaging. Curr Cardiovasc Imaging Rep 2010;3:83–91.
40. Karamitsos TD, Piechnik SK, Banypersad SM, et al. Noncontrast T1 mapping for the diagnosis of cardiac amyloidosis. J Am Coll Cardiol 2013;6:488–497.
41. Banypersad SM, Sado DM, Flett AS, Gibbs SD, Pinney JH, Maestrini V, Cox AT, Fontana M, Whelan CJ, Wechalekar AD, Hawkins PN, Moon JC. Quantification of myocardial extracellular volume fraction in systemic AL amyloidosis: An equilibrium contrast cardiovascular magnetic resonance study. Circ Cardiovasc Imaging 2013;6:34–39.
42. Bandula S, Banypersad SM, Sado D, et al. Measurement of Tissue interstitial volume in healthy patients and those with amyloidosis with equilibrium contrast-enhanced MR imaging. Radiology 2013;268:858–864.
43. Sado DM, White SK, Piechnik SK, et al. Identification and assessment of Anderson-Fabry disease by cardiovascular magnetic resonance noncontrast myocardial T1 mapping. Circ Cardiovasc Imaging 2013;6(3):392–398.
44. Sado DM, Maestrini V, Piechnik SK, et al. Noncontrast myocardial T1 mapping using cardiovascular magnetic resonance for iron overload. J Magn Reson Imaging 2014;6:329–398.
45. Anderson LJ. Assessment of iron overload with T2* magnetic resonance imaging. Prog Cardiovasc Dis 2011;54:287–294.
46. Namdar M, Steffel J, Vidovic M, et al. Electrocardiographic changes in early recognition of Fabry disease. Heart 2011;97:485–490.
47. Ellervik C, Tybjaerg-Hansen A, et al. Haemochromatosis genotype and iron overload: Association with hypertension and left ventricular hypertrophy. J Intern Med 2010;268:252–264.
48. Detterich J, Noetzli L, Dorey F, et al. Electrocardiographic consequences of cardiac iron overload in thalassemia major. Am J Hematol 2012;87(2):139–144.
49. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. Circulation 1991;83:1849–1865.
50. Choi YH, Cowan DB, Moran AM, et al. Myocyte apoptosis occurs early during the development of pressure-overload hypertrophy in infant myocardium. J Thorac Cardiovasc Surg 2009;137:1356–1362.

51. Jekell A, Malmqvist K, Wallén NH, et al. Markers of inflammation, endothelial activation, and arterial stiffness in hypertensive heart disease and the effects of treatment: Results from the SILVHIA study. J Cardiovasc Pharmacol 2013;62:559–566.
52. Turkbey EB, McClelland RL, Kronmal RA, et al. The impact of obesity on the left ventricle: The Multi-Ethnic Study of Atherosclerosis (MESA). J Am Coll Cardiol 2010;3:266–274.
53. Shah RV, Abbasi SA, Neilan TG, et al. Myocardial tissue remodeling in adolescent obesity. J Am Heart Assoc 2013;2:e000279.
54. Weber KT. Cardiac interstitium in health and disease: The fibrillar collagen network. J Am Coll Cardiol 1989;13:1637–1652
55. Hein S, Arnon E, Kostin S, et al. Progression from compensated hypertrophy to failure in the pressure-overloaded human heart: Structural deterioration and compensatory mechanisms. Circulation 2003;107:984–991.
56. Gaudesius G, Miragoli M, Thomas SP, et al. Coupling of cardiac electrical activity over extended distances by fibroblasts of cardiac origin. Circ Res 2003;93:421–428.
57. Nguyen TP, Xie Y, Garfinkel A, et al. Arrhythmogenic consequences of myofibroblast-myocyte coupling. Cardiovasc Res 2012;93:242–251.
58. Kellman P, Wilson JR, Xue H, et al. Extracellular volume fraction mapping in the myocardium, part 2: Initial clinical experience. J Cardiovasc Magn Reson 2012;14:64.
59. Mewton N, Liu CY, Croisille P, et al. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. J Am Coll Cardiol 2011;57(8):891–903.
60. Rubinshtein R, Glockner JF, Ommen SR, et al. Characteristics and clinical significance of late gadolinium enhancement by contrast-enhanced magnetic resonance imaging in patients with hypertrophic cardiomyopathy. Circ Heart Fail 2010;3:51–58.
61. Azevedo CF, Nigri M, Higuchi ML, et al. Prognostic significance of myocardial fibrosis quantification by histopathology and magnetic resonance imaging in patients with severe aortic valve disease. J Am Coll Cardiol 2010;56:278–287.
62. Green JJ, Berger JS, Kramer CM, et al. Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy. J Am Coll Cardiol 2012;5:370–377.
63. Moon JC, Messroghli DR, Kellman P, et al. Society for Cardiovascular Magnetic Resonance Imaging; Cardiovascular Magnetic Resonance Working Group of the European Society of Cardiology: Myocardial T1 mapping and extracellular volume quantification: A Society for Cardiovascular Magnetic Resonance (SCMR) and CMR Working Group of the European Society of Cardiology consensus statement. J Cardiovasc Magn Reson 2013;15:92.
64. Flett AS, Sado DM, Quarta G, et al. Diffuse myocardial fibrosis in severe aortic stenosis: An equilibrium contrast cardiovascular magnetic resonance study. Eur Heart J Cardiovasc Imaging 2012;13:819–826.
65. Jerosch-Herold M, Sheridan DC, Kushner JD, et al. Cardiac magnetic resonance imaging of myocardial contrast uptake and blood flow in patients affected with idiopathic or familial dilated cardiomyopathy. Am J Physiol Heart Circ Physiol 2008;295:H1234–H1242.
66. Shah RV, Abbasi SA, Neilan TG, et al. Myocardial tissue remodeling in adolescent obesity. J Am Heart Assoc 2013;2:e000279.
67. Ho CY, Abbasi SA, Neilan TG, et al. T1 measurements identify extracellular volume expansion in hypertrophic cardiomyopathy sarcomere mutation carriers with and without left ventricular hypertrophy. Circ Cardiovasc Imaging 2013;6:415–422.
68. Waterhouse DF, Ismail TF, Prasad SK, Wilson MG, O'Hanlon R. Imaging focal and interstitial fibrosis with cardiovascular magnetic resonance in athletes with left ventricular hypertrophy: Implications for sporting participants. Br J Sports Med 2012;46(Suppl I):i69–i77.
69. Shirani J, Pick R, Roberts WC, et al. Morphology and significance of the left ventricular collagen network in young patients with hypertrophic cardiomyopathy and sudden cardiac death. Am J Cardiol 2000;35:36–44
70. Lombardi R, Betocchi S, Losi MA, et al. Myocardial collagen turnover in hypertrophic cardiomyopathy. Circulation 2003;108:1455–1460
71. de Bakker JM, van Capelle FJ, Janse MJ, et al. Slow conduction in the infarcted human heart: "Zigzag" course of activation. Circulation 1993;88:915–926.
72. St John Sutton MG, Lie JT, Anderson KR, et al. Histopathological specificity of hypertrophic obstructive cardiomyopathy. Myocardial fibre disarray and myocardial fibrosis. Br Heart J 1980;44:433–443.
73. O'Hanlon R, Grasso A, Roughton M, et al. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. J Am Coll Cardiol 2010;56:867–874.
74. Wong TC, Piehler K, Meier CG, et al. Association between extracellular matrix expansion quantified by cardiovascular magnetic resonance and short-term mortality. Circulation 2012;126:1206–1216.
75. Tunnicliffe EM, Scott AD, Ferreira P, et al. Intercentre reproducibility of cardiac apparent diffusion coefficient and fractional anisotropy in healthy volunteers. J Cardiovasc Magn Reson 2014;16:31.
76. McGill LA, Ismail TF, Nielles-Vallespin S, et al. Reproducibility of in vivo diffusion tensor cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Cardiovasc Magn Reson 2012;14:86.
77. Flett AS, Sado DM, Quarta G, et al. Diffuse myocardial fibrosis in severe aortic stenosis: An equilibrium contrast cardiovascular magnetic resonance study. Eur Heart J Cardiovasc Imaging 2012;13:819–826.
78. Coelho-Filho OR, Shah RV, Mitchell R, et al. Quantification of cardiomyocyte hypertrophy by cardiac magnetic resonance: Implications for early cardiac remodeling. Circulation 2013;128:1225-1233.
79. Richard S, Leclercq F, Lemaire S, et al. Ca^{2+} currents in compensated hypertrophy and heart failure. Cardiovasc Res 1998;37:300–311.
80. Tomaselli FG, Marban E. Electrophysiological remodeling in hypertrophy and heart failure. Cardiovasc Res 1999;42:270–283.
81. Hill JA. Electrical remodeling in cardiac hypertrophy. Trends Cardiovasc Med 2003;13:316–322.
82. Nattel S, Li D. Ionic remodeling in the heart. Pathophysiological significance and new therapeutic opportunities for atrial fibrillation. Circ Res 2000;87:440–447.
83. Shaw RM, Rudy Y. Ionic mechanisms of propagation in cardiac tissue. Roles of sodium and L-type calcium currents during reduced excitability and decreased gap junction coupling. Circ Res 1997;81:727–741.
84. Sipido KR, Volders PGA, Vos MA, et al. Altered Na/Ca exchange activity in cardiac hypertrophy and heart failure: A new target for therapy? Cardiovasc Res 2002;53:782–805.

85. Thomas SP, Kucera JP, Bircher-Lehmann L, et al. Impulse propagation in synthetic strands of neonatal cardiac myocytes with genetically reduced levels of connexin43. Circ Res 2003;92:1209–1216.
86. Kucera JP, Rohr S, Rudy Y. Localization of sodium channels in intercalated disks modulates cardiac conduction. Circ Res 2002:91:1176–1182.
87. Ouwerkerk R. Sodium magnetic resonance imaging: From research to clinical use. J Am Coll Radiol 2007;4:739–741.
88. Joyner RW. Effects of the discrete pattern of electrical coupling on propagation through an electrical syncytium. Circ Res 1982;50:192–200.
89. Spach MS, Heidlage JF, Dolber PC, et al. Electrophysiological effects of remodeling cardiac gap junctions and cell size. Experimental and model studies of normal cardiac growth. Circ Res 2000;86:302–311.
90. Kucera JP, Rudy Y. Mechanistic insight into very slow conduction in branching cardiac tissue. A model study. Circ Res 2001;89:799–806.
91. Jongsma HJ, Wilders R. Gap junctions in cardiovascular disease. Circ Res 2000;86:1193–1197.
92. Gutstein DE, Morley GE, Tammadon H, et al. Conduction slowing and sudden arrhythmic death in mice with cardiac-restricted inactivation of connexin43. Circ Res 2001;88:333–339.
93. van Rijen HVM, Eckardt D, Degen J, et al. Slow conduction and enhanced anisotropy increase the propensity for ventricular tachyarrhythmias in adult mice with induced deletion of connexin43. Circulation 2004;109:1048–1055.
94. Thomas SA, Schuessler RB, Berul CL, et al. Disparate effect of deficient expression if connexin43 on atrial and ventricular conduction. Evidence for chamber-specific molecular determinants of conduction. Circulation 1998;97:686–691.
95. Danik SB, Liu F, Zhang J, et al. Modulation of cardiac gap junction expression and arrhythmic susceptibility. Circ Res 2004;95:1035–1041.
96. Morley GE, Danik SB, Scott B, et al. Reduced intercellular coupling leads to paradoxical propagation across the Purkinje-ventricular junction and aberrant myocardial activation. PNAS 2005;102:4126–4129.
97. Bacharova L, Mateasik A, Krause R, et al. The effect of reduced intercellular coupling on electrocardiographic signs of left ventricular hypertrophy. J Electrocardiol 2011;44:571–576.
98. Kawamura K, Kashii C, Imamura K. Ultrastructural changes in hypertrophied myocardium of spontaneously hypertensive rats. Jpn Cicr J 1976;40:1119–1145.
99. McCrossan ZA, Billeter R, White E. Transmural changes in size, contractile and electrical properties of SHR left ventricular myocytes during compensated hypertrophy. Cardiovasc Res 2004;63:283–292.
100. Shaw RM, Rudy Y. Ionic mechanisms of propagation in cardiac tissue. Roles of sodium and L-type calcium currents during reduced excitability and decreased gap junction coupling. Circ Res 1997;81:727–741.
101. Gutstein DE, Morley GE, Vaidaya D, et al. Heterogeneous expression of gap junction channels in the heart lead to conduction defects and ventricular dysfunction. Circulation 2001;104:1194–1199.
102. Wiegerinck RF, Verkerk AO, Belterman CN, et al. Larger cell size in rabbits with heart failure increases myocardial conduction velocity and QRS duration. Circulation 2006;113:806–813.
103. Main MC, Bryant SM, Hart G. Regional differences in action potential characteristics and membrane currents of guinea-pig left ventricular myocytes. Exp Physiol 1998;83:747–761.
104. Belardinelli L, Antzelevitch C. The role of sodium channel current in modulating transmural dispersion of repolarization and arrhythmogenesis. J Cardiovasc Electrophysiol 2006;17(Suppl1):S79–S85.