This has been a remarkable year of advances in heart failure (HF). There have been many achievements, including updates of various clinical guidelines (1), formal recognition of advanced HF and cardiac transplantation as a subspecialty by the American Board of Internal Medicine (2), and new findings in a number of clinical trials. In this review, we highlight some of the major developments in the field of HF that occurred over the past year.

**Epidemiology**

Recent epidemiologic data have drawn attention to the importance of preventing HF by implementing lifestyle modifications long before HF is manifested. The Health ABC (Health Aging, Body, and Composition) study observed an incidence of 13.6 cases of HF per 1,000 person-years in the elderly population, with men and black participants being more likely to develop incident HF. Interestingly in this contemporary cohort, a large proportion of the HF mortality and rehospitalizations were associated with modifiable risk factors. This observation was also made in the Physicians’ Health Study. In this study of 20,900 middle-age healthy men, those who had normal body weight, never smoked, got regular exercise, drank alcohol in moderation, and consumed breakfast cereal and fruits and vegetables had an associated lower lifetime risk of developing HF (3).

Racial and sex differences in the development and progression of HF have been explored in several publications. In the Health ABC study, 6 of 8 modifiable risk factors (smoking, increased heart rate, coronary heart disease, left ventricular hypertrophy, uncontrolled blood pressure, and reduced glomerular filtration rate) were more prevalent in black participants compared with white participants (4), especially in the younger patient population (5). It is alarming that up to 1 in 100 black men and women age <50 years may develop HF, with hypertension and renal failure as the major determinants. However, the strongest deter-

minant of prognosis in patients hospitalized for HF was neither race nor sex, but advancing age (6,7).

**Pathophysiology**

**Microribonucleic acid (miRNA).** A growing body of literature has provided evidence of the potentially important role that miRNA may play in the pathophysiology of HF and cardiac hypertrophy (8,9). The miRNAs are single-stranded noncoding ribonucleic acid molecules of 21 to 23 nucleotides in length that are transcribed from the genome, but serve to regulate gene expression and cross-talk via modulation of messenger ribonucleic acid signaling instead of translation into proteins (10). Differential expressions of several miRNAs have been observed between normal and cardiomyopathy tissues (11), and changes in miRNA expression have also been observed after ventricular unloading with mechanical assist devices (12,13). Because each miRNA can be linked to an array of downstream processes, the potential for manipulating such signals to reverse pathologic phenotypes is promising, as has been demonstrated in proof-of-concept studies (14). In essence, they may provide potential targets of therapy to delay or reverse cardiac remodeling or fibrosis.

**Modified natriuretic peptides.** Several important observations have also emerged regarding the dynamic adaptations that occur in HF, particularly regarding the great diversity of the natriuretic peptide system. An alternative-splicing protein modified from B-type natriuretic peptide has been identified in patients with advanced HF. These peptides have moderate vasodilatory effects, yet provide for preserved or enhanced renal natriuretic effects (15). Another mutant atrial natriuretic peptide found in humans is noted to be associated with enhanced diuretic, natriuretic, and vasodilatory effects relative to the wild-type peptide (16). As disease progresses, detection of endogenous natriuretic peptides may appear to be reduced in part because of the presence of alternative forms (many of which have reduced bioactivity). This may actually represent a relative deficiency rather than a surplus of natriuretic peptide function (17). These observations have greatly expanded our understanding of the importance and diversity of the natriuretic peptide system (either adaptive or maladaptive), and we can expect more to come.
Stem cell therapy in HF. Recent interest in the stem cell field has involved resident cardiac stem cells that can differentiate into multiple cell types, including cardiac myocytes (18). A small proportion or side population of stem cells express the cell surface markers Kit and Sca1 (19), and such cells can generate cardiomyocytes in vitro and in vivo. Another side population expresses the transcription factor Isl1, allowing the cell to differentiate into endothelial, endocardial, smooth muscle, conduction system, right ventricular, and atrial myogenic lineages during embryonic heart development (20). The cardiac stem cells can now be isolated and expanded from human myocardial biopsy samples. So-called induced pluripotent stem cells can be created to resemble embryonic stem cells and offer potential autologous regenerative therapies (21). Such cells require 3 or 4 specific transcription factors (a sort of reprogramming cocktail) and in principle can generate all mammalian cell types. The processes of isolation, delivery of cells, survival and proliferation, electromechanical integration, and stability with safety are proving to be a big challenge, but several new human protocols are currently underway in the U.S. under the National Institutes of Health clinical trials network model. Despite improvement in our understanding of the biology, clinical trials to date have provided very modest results. Clearly, much more work is needed, both at the bench and in the clinic.

New insights in cardiorenal physiology. Observations from several groups have verified venous congestion to be an important contributor to the cardiorenal syndrome, both in stable patients with chronic HF (22) as well as in patients with advanced HF admitted to the hospital for acute decompensation (23). The venous congestion concept is a complementary view that accompanies the traditional renal–arterial underperfusion doctrine. Recognition that increased right atrial pressure is driving at least some of the problem has catalyzed a closer interdisciplinary look at how to best relieve congestion. A balance of pharmacologic as well as extracorporeal fluid removal techniques, particularly when the natriuretic response to diuretic therapy has diminished (24), has now emerged. Also, tubular function and renal perfusion have been subjects of interest, with an observed inverse relation between urinary excretion of aminoterminal pro–B-type natriuretic peptide (NT–proBNP) and plasma NT–proBNP, and a direct relation between urinary excretion of NT–proBNP and renal plasma flow (independent of glomerular filtration) (25).

Meanwhile, the concept of arterial underperfusion has not been forgotten, and delivery of natriuretic peptide via a specialized catheter has demonstrated enhancement of glomerular filtration and urinary sodium excretion (26). Because the determinants of arterial underperfusion can be multifactorial, another important proof-of-concept human experiment recently has been performed (27). This new procedure was performed using a selective renal sympathetic ablation technique with a localized catheter-based system in patients with severe, refractory hypertension, which resulted in a significant and sustained reduction in blood pressure. It would be of interest to explore these new techniques in patients with advanced HF unresponsive to aggressive diuretic therapy, because renal artery constriction is known to occur.

Evaluation of HF

Natriuretic peptide testing. One of the most important advances this year focused on the possible expanded use of natriuretic peptide testing to help guide medical therapy in patients with HF. First, the TIME–CHF (Trial of Intensified versus Standard Medical Therapy in Elderly Patients with Congestive Heart Failure) study randomized 499 subjects >60 years of age to NT–proBNP–guided versus symptom–guided therapy. Investigators found no significant differences in survival or all-cause hospitalizations between the 2 groups, but some benefits were seen in the 60- to 75-year-old age group (28). Similarly, the PRIMA (Effect of NT–proBNP Guided Treatment of Chronic Heart Failure) study randomized 345 subjects (of 2,900 screened hospitalized patients with elevated NT–proBNP ≥1,700 pg/ml) to an algorithmic approach that triggered an immediate intensification of HF treatment any time a patient's NT–proBNP value exceeded an individualized target versus standard of care. The NT–proBNP–guided arm did not show a significant difference in days alive outside the hospital compared with that guided by symptoms (29). These findings are concordant with preliminary results reported from several smaller single-center studies, and highlight the lack of data supporting the use of natriuretic peptide testing to direct specific therapy. Nevertheless, there is still great interest in this strategy, with more studies likely to be done.

The question of how to best interpret natriuretic peptide levels in patients with HF has been raised by some investigators. In terms of serial measurements, preliminary data from the PRIMA study identified that almost 80% of patients reached their individualized target goal within the follow-up period of 1 year after hospital discharge (29). Furthermore, better outcomes were observed among the 58% who maintained NT–proBNP target ranges for >75% of outpatient visits compared with those who did not maintain target ranges (29). Clearly, changes in natriuretic peptide levels can track with long-term prognosis, as illustrated in an elegant analysis from the Val–HeFT (Valsartan in Heart Failure Trial) (30). In clinical practice, there seems to be a diminishing incremental value as natriuretic peptide levels rise above a certain threshold, yet only large reductions (>80% decrease) seem to favorably alter the long-term prognosis in patients with advanced HF (31).

Novel biomarkers. Although many novel biomarkers continue to search for clinical utility, some circulating metabolic and nutritional biomarkers that are available in clinical practice have been associated with long-term prognosis in the syndrome of HF. These include low serum estradiol (32)
and testosterone (33) levels, high serum cobalamin (34) levels, as well as vitamin D deficiency (35) and low high-density lipoprotein (36) levels, to name a few. Low levels of coenzyme Q have also been associated with a poor prognosis in HF (37). In addition, the presence of albuminuria has been identified as another strong prognostic marker of poor outcome that may reflect underlying vascular pathobiology. In a CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) substudy, the urine albumin–creatinine ratio was measured at baseline and during follow-up of 2,310 patients with HF. Investigators found that 30% had microalbuminuria and 11% had macroalbuminuria, regardless of impaired or preserved left ventricular function. The presence of any albuminuria was independently predictive of adverse cardiac events (38).

Although the prognostic role of many novel markers such as ST2 and galectin-3 continues to be explored in HF (39–41), there is more focus on biomarker predictors of HF development. In an elderly cohort of the Framingham Heart Study, high serum leptin levels were associated with increased risk of developing HF, although these levels had limited prognostic potential beyond clinical variables (42). In contrast, resistin levels have been predictive of development of HF in several cohorts (43,44). Metabolic syndrome has also been implicated as a risk factor for HF (45). An impaired fasting glucose level itself does not seem to be a strong risk factor for development of HF independent of its risk for appearance of subsequent diabetes mellitus (46). Myeloperoxidase (47), interleukin-6 (48), and uric acid (49) have emerged as predictors of HF development in large epidemiologic databases. These observations validate to some extent the important concept that enhanced oxidative stress and inflammation may contribute to the development of HF independent of coronary events.

Genetic testing. We have witnessed broader availability of clinical genetic testing for specific cardiomyopathies in recent times, which coincides with the 50th anniversary of the first clinical description of hypertrophic cardiomyopathy (50). With the availability of genetic data, we are beginning to recognize that different sarcomeric mutations may be associated with different phenotypic expression patterns. In particular, a more significant disruption of myofilament architecture results from a frame-shift mutation rather than a missense mutation, which may explain different patterns of diastolic abnormalities with different gene mutations (51). These findings imply that knowledge of specific mutations may someday provide valuable phenotype prediction and possibly even targeted therapeutic considerations.

Practice guidelines regarding genetic evaluation of cardiomyopathies have been published this year (52). In general, the guidelines have emphasized the strong evidence that exists for genetic determinants of hypertrophic cardiomyopathy and arrhythmogenic right ventricular dysplasia. In the setting of dilated cardiomyopathy, conduction diseases and arrhythmia may point to specific etiologies, such as lamin A/C mutations, that portend a poor prognosis (53).

Hence, considerations for earlier device therapy in such patients may be warranted (52). It is important to recognize that although identification of a specific genetic mutation is helpful in determining subsequent risks of mutation carriers among family members, the absence of any detectable mutation in the genes tested does not imply a truly negative result because the causative mutation may be unknown. In other words, low test sensitivity remains a hurdle for some disease conditions. Regardless of phenotype, genetic and family counseling is strongly recommended and a comprehensive family history must be captured. Education regarding disease transmission and family risk should be provided (52). The guidelines also have highlighted the need for clinical screening, which includes history and physical examination, echocardiogram, and electrocardiogram, as well as some specific testing for certain cardiomyopathies, at regular intervals.

Management of HF

Guideline updates. A broad range of clinical guidelines from major professional societies have emerged this year, but the new recommendations are more refinements than major overhauls. In both the European and American guideline updates, broader adoption of natriuretic peptide testing was recommended based on emerging supportive data, even though much emphasis has focused on diagnostic evaluation of patients in the acute setting. There have been some upgraded recommendations on the use of add-on vasodilator therapy based on the data from the A-HeFT (African American Heart Failure Trial), with new observational studies suggesting the potential incremental benefit of add-on hydralazine plus isosorbide dinitrate beyond African Americans (54). Expansion of device therapy also has been incorporated, with simplification of inclusion criteria to left ventricular ejection fraction (LVEF) \(\leq 35\%\). The emphasis of rhythm control in patients with HF and atrial fibrillation has been relaxed based on neutral data from the AF-CHF (Atrial Fibrillation in Congestive Heart Failure) trial (55). Meanwhile, in the absence of positive data, recommendations regarding the treatment strategies for heart failure with preserved ejection fraction (HFP EF) have remained largely unchanged. Some refinements in diagnostic criteria regarding the evaluation of diastolic dysfunction have been proposed by the American Society of Echocardiography (56). The American guidelines have added an expanded discussion on the appropriate management of hospitalized patients with HF, which consists largely of expert opinion with the emphasis on maintaining or initiating evidence-based pharmacologic therapies during acute exacerbations as tolerated.

Device therapy for HF. Cardiac resynchronization therapy (CRT) continues to be an important treatment for patients with advanced HF. The major focus this year has been the exploration of potential expansion of the standard clinical indications. Two important studies have been reported this
year. First, the 24-month follow-up of the European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial has provided an important demonstration of reverse remodeling and clinical improvement using a composite response end point. The use of CRT provided a beneficial response in patients with an LVEF ≤40% and a QRS duration ≥120 ms but with only mild (New York Heart Association functional class I to II) symptoms (57). The likelihood of left ventricular reverse remodeling was the highest in those with nonischemic etiology or with significant conduction or mechanical delay. The recently published MADIT-CRT (Multicenter Automatic Deﬁbrillator Implantation Trial with Cardiac Resynchronization Therapy) demonstrated a 34% relative risk reduction in death or HF events and reverse remodeling with CRT plus deﬁbrillator compared with deﬁbrillator alone in 1,820 subjects with LVEF ≤30% and QRS duration ≥130 ms (Fig. 1). The beneﬁts were largely driven by reduction in HF events, particularly in those with QRS duration ≥150 ms (58). These landmark ﬁndings secure the role of CRT as a standard therapy for patients with signiﬁcant conduction delays across the symptom spectrum of chronic systolic HF. However, unlike drug therapy, CRT is invasive and expensive; therefore, it may be subject to further scrutiny despite the demonstrated clinical beneﬁts and corresponding reversal of left ventricular remodeling. There will likely be some debate in the months ahead (both in guideline revisions as well as reimbursement decisions) regarding the pros and cons of adopting the traditional rule of honoring the exact inclusion/exclusion criteria from the trial evidence, versus stronger endorsement for only those responder subgroups (i.e., those with wide QRS duration, predominantly ≥150 ms).

One of the major limitations in device trials has been the assumption that once implanted, CRT will deliver an equivalent beneﬁt regardless of settings or device functionalities. Optimization of CRT has been widely discussed and tested with sophisticated imaging techniques, but a stepwise review of several simple parameters (such as ensuring appropriate lead placement, maximizing percent biventricular pacing, detecting and treating underlying arrhythmia, optimizing atrioventricular delay, as well as providing appropriate HF disease management) may provide beneﬁt in a subgroup of nonresponding CRT patients (59). The ability of an imaging modality to select the appropriate candidates for CRT and predict response has been a notion without direct demonstration (60).

**Exercise training in HF.** Simple assessment of exercise endurance continues to be a useful prognostic tool in this population (61), and the lack of improvement after a training program portends a poor prognosis (62). However, the potential risks and beneﬁts of high-intensity exercise training have been unclear. Subjects in the National Institutes of Health-sponsored HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) received either usual exercise recommendations or a structured program in-
management of myocarditis remains mostly empirical. After advances in the treatment of other viral-mediated diseases, the potential for reducing viral burden within the myocardium in those patients with so-called viral persistence is still considered a testable hypothesis. In the BICC (Beta-Interferon in Chronic Viral Cardiomyopathy) trial presented at the 2008 American Heart Association annual meeting, improved symptoms and reduced viral load (including adenovirus, enterovirus, and/or parvovirus) in endomyocardial biopsy samples of 143 patients was more likely to be associated with beta-interferon treatment than placebo. However, there were no differences or changes in cardiac structure or myocardial performance between groups, even though beta-interferon therapy appeared safe (65). Because viral persistence has yet to be linked to an inferior prognosis (66), the benefits of an antiviral therapeutic strategy remain in question, particularly with the need for invasive evaluation and the high cost of therapy.

Meanwhile, for those patients with no evidence of viral persistence, a new randomized study suggests that immunosuppression therapy may provide some benefit. In the TIMIC (Tailored Immunosuppression in Inflammatory Cardiomyopathy) trial, 85 subjects with chronic left ventricular systolic dysfunction and evidence of ongoing myocardial inflammation were randomized to receive azathioprine plus prednisone versus placebo. Additional immunosuppressive therapy was associated with a greater degree of reverse remodeling when compared with placebo in addition to at least 6 months of standard medical therapy (67). These data are indirectly consistent with the positive mechanistic data on reduction of infarct size observed with cyclosporine infusion at the time of percutaneous coronary intervention during acute myocardial infarction (68), illustrating the importance of ongoing immune activity in the progression of cardiac dysfunction.

**Treating HFpEF.** The highly anticipated I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction) trial randomized 4,128 patients age ≥60 years with symptomatic HFpEF (LVEF >45%) to receive irbesartan or placebo. This large and well-executed trial in patients already receiving extensive background therapy found no incremental benefit of irbesartan in the end points of mortality or HF hospitalizations (69) (Fig. 2). This was a disappointing outcome. The findings of I-PRESERVE have also reinforced our concept that HFpEF is distinctly different than systolic HF in ways that are not yet fully appreciated.

**Pulmonary and systemic vasodilators.** Expanded indications for phosphodiesterase 5 inhibitors for moderately symptomatic patients with pulmonary hypertension have been supported by several studies showing improved functional capacity and reduced pulmonary vascular resistance. Meanwhile, the presence of preserved transpulmonary natriuretic peptide uptake coupled with diminished cyclic guanosine monophosphate release has been observed in patients with pulmonary hypertension associated with left heart diseases. These observations suggest a relative deficiency of downstream mediators of vasodilator response in patients with increased pulmonary vascular resistance. They also support the potential benefit of phosphodiesterase 5 inhibitors or newer soluble guanylate cyclase activators (cinaciguat or BAY 58-2667) in combination with nitric oxide donors (70–72). Several ongoing clinical studies are exploring the potential therapeutic benefits of such agents.

With the persistent promise of endogenous vasodilator peptides as potential therapeutic agents, relaxin (a pregnancy hormone produced to inhibit uterine contraction that facilitates the softening and lengthening of the cervix and the pubic symphysis during childbirth) is being evaluated. In 234 subjects with normal to high blood pressure, intravenous relaxin resulted in rapid and sustained improvement in dyspnea and favorable trends toward improved rates of cardiovascular death and HF rehospitalization at 60 days (3% to 10% vs. 17%, p = 0.06), and lower cardiovascular death rates (0 to 6% vs. 14%, p = 0.04) within a mean follow-up of 4.5 months (73). Further early-phase clinical trials on this and several other endogenous vasodilator compounds will soon be underway.

**Renal-sparing therapies.** The search for renal protective agents persists, as worsening renal function continues to be a major comorbidity and impediment to effective treatment for acute decompensated HF. This year we witnessed the formal approval of the first oral drug that antagonizes the vasopressin system, tolvaptan. Its role in preserving renal function remains largely unclear, but tolvaptan does improve hyponatremia under some conditions. Tolvaptan appears to generate an aquaresis without significant hemodynamic effects (74). Another promising candidate drug class, adenosine A1 receptor antagonists, has encountered major hur-
Pharmacological inotropic support. Pharmacologic support for end-stage (stage D) HF remains a challenge. Once a patient is deemed inotropic-dependent, the prognosis is poor and the choice of chronic inotropic drug infusions (dobutamine or milrinone) does not seem to affect long-term outcomes (76). The search for a safe and effective vasoactive drug continues, and the final publication for the ESSENTIAL (Studies of Oral Enoximone Therapy in Advanced Heart Failure) trial highlights the challenges in studying a drug therapy for this patient population, as enoximone yielded a neutral outcome (77). Meanwhile, another approach using a drug called istaroxime that inhibits sodium–potassium adenosine triphosphatase activity while stimulating the sarcoplasmic reticulum calcium adenosine triphosphatase isoform 2 has been examined in the HORIZON-HF (Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime, a Novel Intravenous Inotropic and Lusitropic Agent: a Randomized Controlled Trial in Patients Hospitalized with Heart Failure) (78). The administration of intravenous istaroxime resulted in rapid hemodynamic improvement with a corresponding reduction in heart rate and improvement in echocardiographic indexes of diastolic function. However, like many prior vasoactive drugs, the road to approval is long and treacherous.

Surgical management for advanced HF. Hypothesis 2 of the STICH (Surgical Treatment for Ischemic Heart Failure) trial was published this year (79). It showed a lack of benefit for surgical ventricular reconstruction (SVR) (or modified Dor procedure) in the setting of coronary artery bypass surgery for patients showing systolic HF (LVEF ≤35%) and anteroapical dysfunction. This occurred despite a greater reduction in indexed left ventricular systolic volume in the SVR group. Some proponents of SVR may still believe that there was a selection bias against enrollment of those who would benefit from the procedure, whereas others postulate that impaired diastolic distensibility caused by reducing the left ventricular volume may also contribute to the operation’s lack of benefit. Nevertheless, these rather disappointing results provide justification for not routinely performing SVR at the time of coronary artery bypass surgery.

Novel devices. Several devices tackling novel concepts of HF care have been tested in multicenter clinical trials. The MOMENTUM (Multicenter Trial of the Orqis Medical Cancion System for the Enhanced Treatment of Heart Failure Unresponsive to Medical Therapy) was published this year, and indicates relatively neutral findings using a novel continuous-flow augmentation device for severe acute HF (80). Results of a multicenter study on the safety and efficacy of another novel implantable device that delivers nonexcitatory electrical signals during the refractory period to improve cardiac contractility (cardiac contractility modulation [CCM]) also were presented this year. The FIX-HF-5 (Evaluation of the Safety and Efficacy of the OPTIMIZER System With Active Fixation Leads in Subjects With Heart Failure Resulting From Systolic Dysfunction) study randomized 428 patients with advanced HF (LVEF ≤35% and narrow QRS) to either CCM or no CCM (81), and found that CCM failed to improve the primary efficacy outcome of the anaerobic threshold (82). However, the investigators observed in a less sick group (New York Heart Association functional class III, LVEF ≤25%, n = 185) that improvement in exercise parameters and quality-of-life scores with CCM was possible (82). Although only hypothesis-generating, these findings are quite intriguing because they provide some indication that this treatment modality requires some reserve for contractile improvement. Regardless, exercise parameters are often difficult end points for clinical trials to achieve for various reasons that are not well understood.

Mechanical assist devices and destination therapy. The approval of the HeartMate II device (Thoratec Corporation, Pleasanton, California) as a new-generation nonpulsatile ventricular assist device (VAD) has paved the way to a much needed advancement in this arena. Long-term follow-up of patients with the HeartMate II has provided reassuring data regarding its long-term safety and reliability (83). However, gastrointestinal and intracranial bleeding risks have been observed. The nonpulsatile nature of circulatory support has even been associated with acquired coagulopathies in some patients (84). Smaller devices have also emerged, although they are still in early clinical developmental stages (85,86), and pilot studies on less sick patients are in the planning phases. Questions regarding appropriate patient selection, cost effectiveness, perioperative management, and organization of care delivery for VADs will likely continue to pose important challenges and receive ongoing scrutiny (87,88).

Disease management. Increasing HF readmission rates have been the emerging focus of public reporting as a surrogate of quality of care and competency (89). It is often the assumption that many of the readmissions are preventable, and a major initiative has been launched by the American College of Cardiology to reduce the readmissions rate by 20% in 2012 (the Hospital-to-Home campaign). In many cases, readmission rates are undeterred by advances in drug and device therapies. Prediction models for readmis-
Conclusions

It is refreshing to witness a year of exciting advancements in HF. Although the core drug and device therapeutic approaches remain largely unchanged, knowledge gained from this year’s wide range of publications will likely shape the focus of research to come. We may see much more focus on the expanding population of patients with advanced HF who may benefit from devices (both CRT and VAD). It could be in the form of refining patient selection criteria (using biomarkers or other phenotypes) and exploring strategies for post-procedure optimization. Appropriateness of decision-making, knowledge gained from devices and their clinical stability of individual patients (91–93), and even on the setting of diastolic HF (94). However, like any other diagnostic tool, studies to gauge efficacy are difficult to design, and interpretations of unexplained deviations of impedance signals remain a practical challenge.

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