This past year witnessed growth in the area of molecular genetics, biomarkers, device therapies, and clinical measures of performance. Large clinical trials involving new drug therapies have been disappointing, underscoring the fact that it will be increasingly difficult to show incremental value superimposed on currently available effective therapy. In contrast, effective therapies for acute heart failure (HF) syndrome and diastolic heart failure (DHF) are limited. Device therapy is in a state of further refinement, and several very interesting devices are under study. Our ability to stratify risk continues to improve, although much work is still needed to clarify how to reduce such risks effectively.

Pathophysiology

Genetic insights into cardiomyopathies. As increasingly more genetic mutations are being discovered to play a possible role in the pathogenesis of cardiomyopathy, several important phenotype-genotype associations have been reported this year. For example, the restrictive phenotype of hypertrophic cardiomyopathy has been found to carry a poor prognosis if associated with of beta-myosin heavy chain and cardiac troponin I mutations (1). Also, different clinical phenotypes of arrhythmogenic right ventricular dysplasia have been described with desmosomal protein mutations (2,3). In dilated cardiomyopathy, the prevalence of desmin mutations approximates 1% to 2%, and even dysfunction of seemingly intact desmin networks is sufficient to produce the dilated cardiomyopathy phenotype (4). With rapidly evolving and increasingly affordable technological advances, phenotype-genotype correlations will soon yield important clinical applications. Clinical guidelines of genetic testing are already in development (5–7), and will likely be important as commercial genetic testing is in short supply. Considerably more work will be necessary before molecular genetics becomes more “clinician friendly.”

Novel mechanisms of cardiomyopathy. There have been several interesting translational research reports that may have important therapeutic implications. A report in Cell describes mice deficient in a transcription factor STAT3 prone to developing peripartum cardiomyopathy. With this deficiency, misguided processing of prolactin may result in the production of a cleaved antiangiogenic and proapoptotic subform. This 16 kDa prolactin subform may directly cause microvascular ischemia and postpartum oxidative stress (8). In patients with peripartum cardiomyopathy, levels of STAT3 expression are indeed diminished and the 16 kDa prolactin (as well as the activated cathepsin D, the prolactin-cleavage enzyme) can be detected. This new mechanism may have important therapeutic implications because drugs like bromocriptine may block prolactin activity.

Another interesting finding was reported in Nature Medicine this year. There may be a potential extracardiac role for adrenal G-protein-coupled receptor kinase 2 (GRK2). In mice models with HF, high levels of GRK2 are found in the chromaffin cells in the adrenal gland (9), which may cause down-regulation and desensitization of β2-adrenergic receptors. This is similar to that seen in leukocytes in patients with HF (10). Furthermore, delivery of an inhibitor of GRK2 activation (beta-adrenergic receptor kinase inhibitor) can lead to restoration of agonist-mediated inhibition of adrenaline and noradrenaline secretion (9). Therefore, directly targeting adrenal GRK2 inhibition could represent another potential sympatholytic strategy for the treatment of HF. Understanding such mechanisms and the potential biomarkers to distinguish such phenotypes will be of great importance in better profiling of an otherwise poorly differentiated patient population.

Mechanistic understanding of DHF. Several important reports have provided new insights into what has been termed DHF or HF with preserved left ventricular (LV) function. Patients with DHF may also show serologic evidence of an active fibrotic process (in terms of collagen turnover or matrix metalloproteinases activities), which corresponds with the severity of diastolic dysfunction (11). Furthermore, patients with DHF often present with a
preserved force-frequency but an impaired relaxation-frequency relationship, with impairment in left ventricular arterial coupling as heart rate increases (12). As a group, they also have many comorbid conditions that contribute to volume overload (13).

Data from the Olmsted County database suggest that compared with hypertensive or healthy control subjects, patients with DHF have more impaired renal function, despite smaller end-diastolic volumes, lower cardiac output, higher end-diastolic pressures, and more impaired arterial relaxation with increased diastolic stiffness (Fig. 1) (14). Careful evaluation of echocardiographic data reveals that patients with DHF have accentuated left ventricular hypertrophy and left atrial dilation or failure (15). Evaluation of the ratio of mitral E wave and tissue Doppler E′ wave at the lateral mitral annulus can also reliably identify the presence of DHF (15,16). The reliability of these echocardiographic indices as surrogate markers for treatment responses remains unclear.

Autoimmunity in dilated cardiomyopathy. A resurgence of interest in the clinical role of autoimmunity in dilated cardiomyopathy comes with the publication of several observations regarding the role of autoantibodies directed against cardiac beta1-adrenergic receptors (17). In particular, patients with these autoantibodies seem to have greater improvement after beta-blocker therapy (18). It is likely that part of the immunoglobulin may bind to cardiac antigens, while another portion might trigger the negative inotropic effects via corresponding receptors identified on cardiomyocytes (19). However, despite the implications of viral involvement in dilated cardiomyopathy, the presence of viral genome has yet to consistently translate into functional alterations that cause the pathogenesis of dilated cardiomyopathy (20). Yet, in family members of patients with dilated cardiomyopathy, cardiac autoantibodies are independent predictors of disease development within 5 years (21). These observations may justify the continuing exploration of immunoadsorption therapy or strategies that identify cardiomyopathies with an underlying autoimmune mechanisms (22), even though treatment strategies targeting global or specific inflammatory processes to date have been disappointing in the absence of targeted patient selection.

Evaluation and Monitoring

Biomarker evaluation in HF. Natriuretic peptide testing remains the primary focus of publication. The confirmation of the clinical and cost effectiveness of natriuretic peptide testing can be found in the prospective Canadian IMPROVE-CHF (Improved Management of Patients With Congestive Heart Failure) study, in which patients randomized to management strategy guided by amino terminal pro-B-type natriuretic peptide (NT-proBNP) testing in the IMPROVE-CHF trial (area under the curve for logistic model combining NT-proBNP and clinical judgment improved to 0.904 from 0.834 to 0.855 with either one alone). p value was obtained by comparing 2 logistic models. AUC = area under the receiver-operating characteristic curve.
independent risk factor for mortality (25,26). Beyond establishing diagnosis during hospital admissions, serial BNP and cardiac troponin testing also may provide important prognostic information in the ambulatory care setting (27). Still there are some concerns regarding the day-to-day variability with serial testing (28–30), and precisely how clinicians should utilize these biomarkers for risk prediction in their daily clinical practices is still open to some debate. Risk stratification is a wonderful concept, but how do we actually use this information in clinical practice? Does “high risk” mean that treatment should change? Can these biomarkers be used to decide when to hospitalize or when to discharge a patient? Consensus guidelines supporting the diagnostic and prognostic value of natriuretic peptide testing have recently been published (31), outlining emerging areas of potential BNP testing such as population screening, combination with other biomarkers, and BNP-guided strategies for patient management.

Several interesting new biomarkers are in the early stages of development. Surrogates of renal insufficiency including the old standard blood urea nitrogen and the newer biomarker cystatin C are emerging as important prognostic markers (32,33). The clinical significance of altered forms of natriuretic peptides (34,35) are still under intense study. Recent data have also confirmed the association between increased serum concentrations of high-sensitivity C-reactive protein and functional limitation and prognosis (but not to the severity of left ventricular ejection fraction) (36). Expression of myeloperoxidase (a leukocyte-derived enzyme associated with oxidative stress) (37) and growth differentiation factor-15 (a member of the transforming growth factor beta family) (38) also are increased in patients with chronic HF. Both provide prognostic value in this population incremental to natriuretic peptides (39,40). In a similar manner, ST2 (a member of the interleukin-1 receptor family) has shown prognostic discrimination beyond natriuretic peptide levels in acute HF (41). However, the lack of a standardized, readily available commercial assay for many of these new biomarkers and their wide variabilities may limit their broad clinical application.

**Predicting arrhythmic risks in HF with microvolt T-wave alternans (MTWA).** The ABCD (Alternans Before Cardiac Defibrillator) trial suggested that either a negative electrophysiological study or negative MTWA had a 95% negative predictive value for predicting future arrhythmic events up to 2 years, but serial testing may be warranted. It is estimated that the number needed to treat with a defibrillator for 2 years to save 1 life is 9 among non–MTWA-negative patients (vs. 76 among MTWA-negative patients) (42). If these findings are validated prospectively, MTWA may provide greater confidence in reassuring a low arrhythmic risk with potential deferment of defibrillator implantation (43,44).

**Device-based remote monitoring in HF.** Utilizing intrathoracic impedance measurements, 2 large European studies have validated the potential for an alert-based remote monitoring system (45,46). Devices that directly measure left atrial or pulmonary artery pressures may also provide a reliable assessment of hemodynamic status. Preliminary data from the Australia–New Zealand feasibility study were presented this year in patients who received an implanted left atrial pressure (LAP) monitoring device with treatment algorithms guided by LAP measurements. This open-label study found fewer episodes of elevated LAP >25 mm Hg when guided by LAP measurements than when blinded. There also was higher utilization of neurohormonal antagonists, with lower doses of diuretics and unchanged serum creatinine levels, in the LAP-guided group (47). Newer devices also are emerging, some featuring implantation of pressure sensors directly at the level of the pulmonary artery (48,49). Similar to biomarker testing, the challenge here will be to identify effective therapeutic interventions that can alter the natural history of disease progression. This will likely require incorporation of specific treatment modalities to monitoring devices. Such protocols, however, are difficult to design, but have a promising future if the costs can be justified by showing improved outcomes.

**Therapy**

**Pharmacologic therapy in chronic HF.** The increasing acceptance of reverse remodeling as a surrogate end point must be tempered against the many vague definitions currently in vogue (50). Important confirmatory studies indicate that a fixed-dose combination of hydralazine/nitrates shows reversal of abnormal cardiac structure and performance (51). There also is evidence showing that patients receiving beta-blockers with their angiotensin-converting enzyme inhibitors switched to candesartan may derive additional structural and functional benefits when spironolactone is added (52). However, these results are in direct conflict with preliminary data from 2 prospective evaluations of LV remodeling effects of aldosterone receptor antagonists in patients with mild-to-moderate HF, in which unexpectedly neither eplerenone nor canrenone were found to offer incremental reversal in LV remodeling over standard therapy (44,53). Although the benefits of spironolactone are based on studies that include patients with post-infarction HF and advanced HF, it is clear that studies of aldosterone receptor blockade in mild-to-moderate systolic HF and DHF still are necessary to justify their broad use.

**Cell-based and gene therapy.** Early-phase stem cell trials continue to be published with reports involving allogeneic mesenchymal stem cells as well as novel delivery systems for autologous skeletal myoblasts in ischemic or post-infarction HF (54,55). Data are promising, but the sample sizes are relatively small and the relative pros and cons for various techniques and cell types remain unsettled. In contrast, studies of gene therapy this year featured 2 targets for adenoviral gene delivery: cardiac S100A1 (calcium-binding protein) (56) and cardiac sarcoplasmic reticulum calcium...
adenosine triphosphatase isoform 2a (57). Both strategies are heading toward human feasibility studies.

**Novel drugs and devices for renal preservation in acute HF.** One of the largest trials published in the HF arena this year involved the use of tolvaptan, a vasopressin V2 receptor antagonist. Following on the successes of the neurohormonal antagonists and the effectiveness of tolvaptan in relieving symptoms and reducing body weight via water removal, the EVEREST (Efficacy of Vasopressin antagonist in Heart Failure Outcome Study with Tolvaptan) (Fig. 3) study was launched as a 4,133-patient multicenter outcomes study to establish the efficacy and safety of tolvaptan in patients with HF (58,59). Reductions in average body weight at day 7 or discharge were statistically significantly better in the tolvaptan group versus the placebo group, but no improvement in patient-assessed global clinical status at day 7 or discharge was seen despite more patients in the tolvaptan groups reporting improvement in dyspnea and edema. Long-term tolvaptan use in the EVEREST study did not differ from placebo in all-cause mortality, HF, or cardiovascular hospitalizations. Despite a relatively neutral study, the EVEREST study did demonstrate safety, and it may have a role in selective patients when loop diuretic therapy is inadequate or inappropriate.

Meanwhile, large phase III trials have been initiated for the intravenous selective adenosine A1 receptor antagonist, rololofylline (KW-3902). Early pilot data confirmed the choice of drug dosing while illustrating a wide variation of treatment patterns in different countries (53). A dose-ranging study using a similar oral compound, BG–9928, also demonstrated significant increases in sodium excretion in patients with stable HF without causing kaliuresis or impairing renal function (60).

The ongoing interest in using devices to treat congested patients also has been challenging. We have learned that ultrafiltration has the potential for removing more sodium per liter with less electrolyte derangement while promoting greater weight and fluid loss than intravenous diuretics. However, compared with generic loop diuretic infusions, the need for invasive vascular accesses and high operative costs still pose great challenges to broad clinical adoption despite fewer rehospitalizations (61).

**Vasodilator therapy in acute HF.** The potential hazards of inotropic therapy are now broadly accepted (62), although the decision to use chronic inotropic therapy is sometimes justified for reducing recurrent hospitalizations and improvement in quality of life in patients with advanced stage D HF (63). Post-hoc analyses from large clinical studies and registries of patients with acute HF continue to support the potential benefits of vasodilator therapy (64). A prospective phase II European study with ularitide, a new natriuretic peptide, showed improvement in the hemodynamic profile without causing renal compromise or adverse clinical outcomes (65). However, chronic intermittent infusion of nesiritide, an approved vasodilator/natriuretic peptide, failed to show benefit over placebo in the FUSION-II (second Follow-Up Serial Infusions Of Nesiritide in Advanced Heart Failure) study. At the end of the trial, there were no significant differences in all-cause mortality or cardiovascular or cardiorenal hospitalization, and changes in renal function were similar (44). Despite being a neutral study, the FUSION-II study provides some reassurance that nesiritide can be safely administered. The study also reaffirms just how difficult it is to improve patients with advanced disease stages who are receiving excellent care.

**Nonpharmacologic therapy.** An age-old question regarding the role of fluid restriction in the management of congestive HF management finally has finally been dealt with in a prospective, single-blind study. Time to clinical stability was compared between patients assigned to fluid restriction and those allowing free access to fluids. No significant differences in outcomes or biochemical measures were found (66).

**Treatment for DHF.** Important clinical trials in patients with DHF have yet to be completed. However, some smaller studies have provided new information. Not surprisingly, lowering blood pressure itself seems to be one of the major determinants in improving diastolic relaxation, re-
Performance Measures

This year also marked the introduction of public access to “report cards” for hospitals across the nation based on their myocardial infarction and HF mortality as well as their adherence to standardized clinical performance measures. However, although the implementation of these measures may provide a logical extension of quality improvement, direct evidence of these performance measures showing long-term benefits are lacking. Recent exploration of the 4 current in-patient performance measures have shown that aside from prescription of an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker at discharge, there is little relationship to patient mortality and combined mortality and re-hospitalization in the first 60 to 90 days after discharge (82). The large OPTIMIZE-HF (Organized Program to Initiate Life-Saving Treatment in Hospitalized Patients With Heart Failure) registry further validated the importance of pre-discharge drug utilization programs for beta-blockers (83). Therefore, better understanding of what recommendations can lead to effective outcomes should precede the decision of policies for quality improvement and assessing performances.

Prevention

An insightful observation from the Framingham group features family history of HF as a risk factor for the development of HF. Not only was there an increase in prevalence in structural abnormalities by echocardiography, but also the age- and gender-adjusted 10-year incidence rates of HF were 2.72% versus 1.62% among offspring with versus those with no family history of HF (84).

Preventive intervention in patients with asymptomatic LV dysfunction has not been widely studied. Two studies using prophylactic carvedilol (85) and enalapril (86) before giving chemotherapy (an at-risk stage A population) were published this year. In patients with antecedent detectable troponin I levels (24% of all patients receiving high-dose chemotherapy), those treated with enalapril showed no evidence of subsequent cardiotoxicity compared with 43% in the control group (86).

Conclusions

Despite some neutral results from pivotal pharmacologic drug and device trials, research in the field of HF remains alive and well. Therapeutic targets, as expected, are becoming more narrowly focused. Devices have been spectacularly successful, but in many cases have been limited by their lack of demonstration of their long-term cost effectiveness and potential cost implications. Newer, highly innovative drugs and devices are on the horizon, but the regulatory process remains tedious, albeit necessary. Prevention is receiving more attention as clinicians realize that HF is largely a preventable disorder. As reflected in all of the contemporary guidelines, what is still lacking is a departure from the
“one-size-fits-all” concept of HF, and the need to appreciate how patients can be profiled, how treatment can be tailored, and how responses and progress can be measured. We look forward to the coming year with great anticipation, realizing that moving beyond our current effective therapies will require more imagination and creative trial methodologies and a better understanding of the differences among patients with HF so that treatment can be better tailored.

Reprint requests and correspondence: Dr. W. H. Wilson Tang, 9500 Euclid Avenue, Desk F25, Cleveland, Ohio 44195. E-mail: tangw@ccf.org.

REFERENCES


