17 CVD ADVANCES
RI Clinicians, Researchers Share Advances in Recognition and Treatment of CVD
BARBARA ROBERTS, MD, FACC
GUEST EDITOR

19 Gender-Specific Aspects of Cardiovascular Disease
BARBARA H. ROBERTS, MD, FACC

23 Takotsubo Cardiomyopathy: A Clinical Review
SADDAM S. ABISSE, MD; ATHENA POPPAS, MD, FACC, FASE

28 Cardiac Magnetic Resonance Imaging and Computed Tomography: State of the Art in Clinical Practice
CHRISTOPHER LANG, MD; MICHAEL K. ATALAY, MD, PHD

35 New Diagnostic and Therapeutic Possibilities For Diastolic Heart Failure
EUY-MYOUNG JEONG, PhD; SAMUEL C. DUDLEY, JR., MD, PhD

38 Transcatheter Aortic Valve Replacement: A Review of Current Indications and Outcomes
WILLIAM PRABHU, MD; PAUL C. GORDON, MD

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February is Heart Health month so it is appropriate that this issue of the Rhode Island Medical Journal is devoted to an update on the field of cardiology. Few specialties have seen such explosive growth in knowledge and the ability to modify disease as has cardiology over the last half century. When I was an intern in 1968–1969, coronary angiograms were new and infrequent, having been described by Cleveland Clinic physicians Drs. Sones and Shirey in 1962. Exactly one of my patients that year was referred for a cardiac catheterization. How times have changed. According to the CDC FastStats, about one million people in the United States had cardiac catheterizations/coronary angiograms in 2010 and an additional 500,000 had a coronary artery intervention. In the 1960s patients with myocardial infarction were treated with morphine and bed rest, and the first statin to be approved by the FDA was still some two decades in the future. While the mortality rate from atherosclerotic cardiovascular disease was decreasing, most of the diagnostic modalities, pharmacologic armamentarium and devices we now take for granted were not available to clinicians.

During my cardiology fellowship years in the early 1970s, echocardiography was in its infancy; a patent for the first MRI machine had just been issued; cardiac valve replacement required open heart surgery and placing the patient on cardiopulmonary bypass, diastolic heart failure was not on anyone’s radar screen; Takotsubo Cardiomyopathy had not been named and percutaneous coronary interventions were still in the future – the first occurred in Switzerland in 1977. Gender-specific aspects of cardiovascular disease were not appreciated and, in fact, coronary heart disease was taught as a disease of men.

CONTRIBUTIONS
This issue of the Rhode Island Medical Journal features articles on various aspects of cardiovascular disease of interest to clinicians. My contribution, “Gender-Specific Aspects of Cardiovascular Disease,” discusses some of the differences in symptoms, risk factors and outcomes between women and men with atherosclerotic cardiovascular disease.

In “Takotsubo Cardiomyopathy: A Clinical Review,” ATHENA POPPAS, MD, FACC, FASE and SADDAM ABISSE, MD, examine this condition, which is increasingly being recognized in patients presenting with an acute coronary syndrome. CHRISTOPHER LANG, MD, and MICHAEL K. ATALAY, MD, PhD, in “Cardiac Magnetic Resonance Imaging and Computed Tomography: State of the Art in Clinical Practice,” review the methodologies of novel MRI and computed tomography modalities, their specific roles in the diagnosis of cardiac pathophysiology, and their utility in outcomes assessment and prognosis for various disease states.

EUY-MYOUNG JEONG, PhD, and SAMUEL C. DUDLEY, JR., MD, PhD, in “New Diagnostic and Therapeutic Possibilities for Diastolic Heart Failure,” discuss symptoms, diagnosis, and therapeutic approaches, along with results of animal research on this condition, which is ongoing in Dr. Dudley’s laboratory.

“Transcatheter Aortic Valve Replacement: A Review of Current Indications and Outcomes” by WILLIAM PRABHU, MD, and PAUL GORDON, MD, discuss this new technique for replacing stenotic aortic valves and report on the experience with the first fifty-six patients to undergo this procedure at Rhode Island Hospital.

In the last half century our understanding of cardiovascular disease has increased enormously, along with our ability to modify the course of what remains the number one killer of men and women, both in the United States and around the globe. One can only imagine what an issue of the 2054 Rhode Island Medical Journal on this same subject would look like.

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ABSTRACT
When William Heberden gave his classic description of angina pectoris in 1768, he inadvertently described a gender-specific difference in heart disease when he noted the predominance of men with this condition. It is only in the last few decades that the medical profession has recognized that women are equally afflicted with atherosclerotic cardiovascular disease, albeit with some differences in presentation, risk factors and outcomes. This article will detail the ways in which men and women differ when it comes to the number one killer in the developed, and increasingly the developing, world.

KEYWORDS: Atherosclerotic cardiovascular disease (ASCVD), Myocardial infarction (MI), Risk factors, Coronary artery bypass graft (CABG)

INTRODUCTION
William Heberden gave an address to the Royal College of Physicians in London in 1768 in which he described a new syndrome he called “angina pectoris,” a Latin term for a strangling or choking in the chest. Though he was unable to determine angina’s cause, he unwittingly made the first observation of gender-specific differences in cardiovascular disease when he wrote: “I have seen nearly a hundred people under this disorder, of which number there have been three women, and one boy twelve years old. All the rest were men near, or past the fiftieth year of their age.”

When the epidemic of atherosclerotic cardiovascular disease (ASCVD) occurred in the twentieth century, the myth that this was a man’s disease persisted. The prototypical patient with angina or myocardial infarction was described as a middle-aged male. Physicians, and women themselves, were slow to realize that atherosclerosis affected both sexes, albeit with differences that have become more apparent over the last few decades. In this article I will review gender differences in risk factors, symptoms, and outcomes in ASCVD.

RISK FACTORS
Dyslipidemia
Little was known about the etiology of ASCVD before the second half of the twentieth century. Ancel Key’s Seven Countries Study in the 1950s correlated dietary saturated fat intake and serum cholesterol levels with the risk of dying of heart disease in the United States (US), Finland, Greece, Serbia, Japan, the Netherlands and Italy. Unfortunately no women were included in Key’s study. The Framingham Heart Study (FHS) was undertaken by the National Institutes of Health in the late 1940s in response to the epidemic of heart disease. Its objective was to identify the risk factors that contribute to the development of ASCVD.

The study recruited 5,209 men and women between the ages of 29 and 62. The subjects returned every two years for detailed physical examinations, life style interviews and blood tests. FHS and other epidemiologic studies around the world led to the identification of the major modifiable risk factors for ASCVD: smoking, hypertension, hypercholesterolemia, diabetes, obesity and sedentary lifestyle. The unmodifiable risk factors include age and family history.

At that time cholesterol metabolism was poorly understood, but with the groundbreaking work of Drs. Robert Levy, Donald Fredrickson, Michael Brown and Joseph Goldstein, the roles of lipoproteins and of lipoprotein receptors in the pathogenesis of atherosclerosis were slowly unraveled. The lipoproteins are classified according to their density, and all lipoproteins with the exception of high-density lipoprotein (HDL) are atherogenic. The first hint that low-density lipoprotein (LDL) might not be as atherogenic in women as men arose from the work of Neil Stone in the US and Joan Slack in England on kindred with Type II Familial Hypercholesterolemia. At equivalent markedly elevated LDL-cholesterol levels, affected women in these families developed signs and symptoms of ASCVD on average 10 to 15 years later than affected men.

Cui and his colleagues followed a cohort of 2,406 healthy men and 2,056 healthy women ages 40 to 64 for an average of 19 years. All had measurements of total cholesterol, LDL-cholesterol, non-HDL-cholesterol, and HDL-cholesterol. Elevations in total, LDL-cholesterol, and non-HDL cholesterol, along with low levels of HDL-cholesterol all correlated with an increased risk of cardiovascular disease (CVD) mortality in men. In women, only low levels of HDL-cholesterol and high levels of non-HDL-cholesterol predicted CVD mortality in women and the relative risk was greater in women than in men. Even at LDL-cholesterol levels of over 190 mg/dl, there was only a small and statistically insignificant increase in a woman’s risk of dying of cardiovascular disease (CVD). And at equivalent LDL-cholesterol...
levels ranging from under 131 mg/dl to over 160 mg/dl, women with HDL-cholesterol under 50 mg/dl had a 3 to 4 four-fold increase in the risk of dying of CVD.

Other studies have looked at triglyceride (TG) levels and the risk of CVD and found that risk in women is increased more than in men as TG increases. With regard to lipids therefore, it appears that LDL cholesterol is less predictive of risk in women than in men, while elevations of non-HDL cholesterol (with which hypertriglyceridemia is closely linked) and low levels of HDL cholesterol are more predictive of risk.

**Smoking**

There is good epidemiologic evidence that smoking is a stronger risk factor in women than men. In a Danish study of smoking and age at first myocardial infarction (MI), smoking lowered the median age of first MI in women from 79 to 60, and in men from 71 to 64 years of age.

Another investigation into smoking risk looked at pooled data from three studies with a total cohort of 11,472 women and 13,191 men who were followed for a mean of 12.3 years. The relative risk of MI in women who were current smokers was 2.24 compared with 1.43 in male smokers. This difference was significant and was unchanged after adjustment for other risk factors. Among women who were under 55, the relative risk of MI was increased almost 7-fold compared to almost 3-fold for same-aged men.

**Diabetes**

Diabetes, like smoking, is a more potent risk factor in women than in men. Kannel and Wilson analyzed Framingham data and found that the age-adjusted relative risk for coronary heart disease (CHD) in diabetic women compared to non-diabetic women was 3.7 (men 1.5), for peripheral arterial disease 6.4 (men 3.4) and for cardiac failure 8.0 (men 4.4). In a 40-year follow-up of the Rancho Bernardo Cohort Study, Dr. E. Barrett-Connor reported that men who had diabetes by history or fasting plasma glucose had a 2.4-fold excess risk of heart disease compared to men without diabetes, and women who had diabetes had a 3.5-fold excess risk compared to women without diabetes; these differences were independent of many covariates.

In summary, while women and men have the same risk factors for ASCVD, smoking, hypertriglyceridemia, low HDL-cholesterol and diabetes impart greater risk to women than men, while elevations of LDL-cholesterol impart more risk to men than women.

**SYMPTOMS**

Gender disparity in the way ASCVD presents was first noted in the Framingham study. In a 26-year follow-up study of the initial participants, a striking difference was found in the ways men and women presented. There were a total of 1,240 coronary events among the initial cohort; these included MI’s, sudden death, angina pectoris and unstable angina. Despite roughly equal numbers of men and women, 60% of these events occurred in men and 40% occurred in women. Among men, acute MI was the most frequent presentation, comprising 43% of men’s initial coronary events, an additional 10% of first events in men were episodes of sudden death. Among women however, angina was the presenting complaint in 53% of women and MI was the initial event in only 29% of women. The authors also noted that once ASCVD was manifest in women they had a greater risk...
of mortality with an MI than did men. This finding has been found in other studies as well. FHS was first to report on the greater likelihood of silent or unrecognized MIs in women compared to men [34% vs 27% respectively].

The Coronary Artery Surgery Study revealed gender discrepancies in anginal prognosis. Among the study population of 20,391 patients, all of whom had coronary angiograms for the evaluation of chest pain (CP), 50% of women compared to 17% of men were found to have minimal or no atherosclerosis.

Because women with angina were less likely than men to have obstructive coronary artery disease (CAD) the Women’s Ischemia Syndrome Evaluation (WISE) investigations were undertaken to optimize symptom evaluation and testing, to explore the mechanisms for symptoms and ischemia in the absence of angiographic coronary stenosis and to investigate the role of reproductive hormones on symptoms. A total of 159 women (out of 323) who had coronary angiograms for chest pain were found to have minimal or no luminal irregularities. Intracoronary adenosine was used to determine the presence or absence of coronary microvascular dysfunction. Seventy-four (47%) had sub-normal coronary flow velocity reserve suggestive of microvascular dysfunction. The authors concluded that this abnormality was present in about half of women who had chest pain in the absence of obstructive CAD.

Despite the absence of coronary obstruction, the WISE investigators observed a high rate of adverse outcomes in these women. They subsequently undertook an intravascular ultrasound (IVUS) study of 100 women with suspected ischemia without obstructive CAD (<50% stenosis). The study showed 69.6% of patients had no (<20% stenosis) and 30.4% had minimal CAD. IVUS investigation in 92 women showed that 21% had no atherosclerosis while in the remaining 79% per cent atheroma volume was 27±8%. The number of risk factors correlated with the percent of atheroma volume and percent of vessel involvement. Seventy-three percent of the women in whom remodeling was assessed had evidence of positive remodeling. These findings were felt to help explain the increased risk of adverse outcomes.

A recent study of sex differences in symptoms in acute coronary syndrome (ACS) among 1,015 patients [30% women] under 55 found that women were significantly more likely than men to have non-ST-segment elevation MI [37.5% vs 30.7%] and to present without chest pain [19.0% vs 13.7%]. Although CP was the most common presenting symptom of ACS, patients without CP were not different from those with CP in type of ACS, troponin level, or coronary stenosis.

Multiple studies have looked at gender differences in symptom presentation with acute MI. In addition to the FHS finding mentioned above, a study from Canada found that women with MI were more likely than men to have atypical symptoms, had a higher prevalence of diabetes and hypertension, and were older. McSweeney and her colleagues administered questionnaires to 515 female survivors of documented MI. Among prodromal symptoms the most common was unusual fatigue, occurring in almost 71% of women. Only 29.7% of women had prodromal chest pain. Acutely, at presentation with MI, the most common symptom was shortness of breath (57.9%). Forty-three percent of women experienced no chest pain and of those who experienced discomfort the most frequent locations were the back (37%) and high chest (27.7%).

Disparate findings were reported from the Myocardial Infarction Triage and Intervention Registry which found no gender differences in symptoms of MI with 99% of 841 men and 99.6% of women presenting with chest pain.

OUTCOMES

Women have a higher mortality than men from MI. Vaccarino and her colleagues abstracted data on over 155,000 women and over 229,000 men entered into the National Registry of Myocardial Infarctions. Overall in-hospital mortality was 16.7% for women and 11.5% for men. Among patients under age 50, women’s mortality was 6.1% compared to 2.9% for same-aged men. The difference in mortality between men and women was no longer significant after age 74. More recent data was reported from 78,254 patients with acute MI in 420 United States hospitals from 2001-2006. In the overall cohort, mortality was 8.2% in women and 5.7% in men. This difference was not statistically significant, but in the ST segment elevation MI cohort, there was a significant difference in mortality, 10.2% in women vs 5.5% in men. In this study, women were less likely to receive early medical and acute reperfusion therapies, timely pharmacological and mechanical reperfusion, and invasive procedures. Women were older than men and had more co-morbidities.

Other studies have found that women have higher operative mortality from coronary artery bypass surgery (CABG). In this retrospective analysis of 15,440 patients who had CABG at 31 Midwestern hospitals, operative mortality [OM] was 4.24% in women and 2.23% in men, p<0.0001. After adjustment for all co-morbidities, even body surface area, female gender remained an independent predictor of increased mortality [risk adjusted OM 3.81% in women and 2.43% in men]. Another review of CABG and percutaneous coronary interventions [PCI] in 2007 examined 23 studies reporting outcomes by gender for CABG and 48 reporting outcomes for PCI. The authors found that the majority of studies noted greater in-hospital mortality in women than men, with mortality differences resolving with longer follow-up.

SUMMARY

Gender differences in ASCVD exist for presenting symptoms, risk factor weighting, and outcomes. More research will hopefully elucidate mechanisms and improve the treatment of women with this disease.
References


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ABSTRACT
Takotsubo cardiomyopathy is a reversible cardiomyopathy which has increasingly been recognized in the differential diagnosis of patients presenting with acute coronary syndrome. It is characterized by transient systolic ventricular dysfunction with regional wall motion abnormalities beyond a single vascular territory and in the absence of significant epicardial coronary artery obstruction. Often, there is an acute emotional or physical stressor immediately preceding the presentation. Classical apical ballooning is seen on ventriculography or echocardiography but variants with isolated basal or mid wall akinesis have been described. Catecholamine excess and cardiotoxicity is the most compelling putative mechanism. The long-term prognosis is excellent but serious complications including cardiogenic shock and arrhythmias may occur acutely. Supportive treatment is the mainstay of therapy.

KEYWORDS: Takotsubo cardiomyopathy (TTC), Apical ballooning syndrome (ABS), Stress Cardiomyopathy

INTRODUCTION
Takotsubo cardiomyopathy (TTC) is also known as broken-heart syndrome, apical ballooning syndrome and stress-induced cardiomyopathy. It is a reversible cardiomyopathy characterized by transient systolic ventricular dysfunction with a clinical presentation indistinguishable from acute myocardial infarction but in the absence of significant coronary artery obstruction.1,2 It is frequently precipitated by sudden, stressful emotional events, but there are also reports of TTC following physiologic stress such as sepsis, non-cardiac surgery, and subarachnoid hemorrhage.2,3,4 This syndrome was reported as early as 1967 in patients under intense emotional stress such as bereavement or after homicidal assault.5,6 In the 1990s, Sato and colleagues coined the term takotsubo cardiomyopathy to describe the unusual shape of the left ventricular during systole.7,8 Typically, the mid to apical segments of the left ventricle are akinetic and the spared, basal walls exhibit compensatory hypercontractility. Takotsubo is a pot with round base and narrow neck used in Japan for trapping octopuses and has a similar appearance to this apical ballooning. TTC occurs most commonly in post-menopausal women and has a very good prognosis. Acutely, patients are often critically ill with heart failure and secondary complications such as left ventricular outflow tract obstruction, and arrhythmias but ventricular dysfunction and symptoms resolve quickly and death is very rare. In this systemic review we will describe the clinical presentation, pathophysiology, prognosis and treatment of this syndrome.

Epidemiology and clinical presentation
Because of increasing awareness of this condition, in 2006 the American Heart Association incorporated TTC into the classification of cardiomyopathies as a primary acquired cardiomyopathy.9 The lack of consensus on a diagnostic criteria and the under-recognition of the disease makes it challenging to estimate the true prevalence of TTC. The best estimates come from several studies looking at consecutive patients presenting to the hospital with suspected acute coronary syndrome or myocardial infarction. Here, it has been reported to account for 1-3% of all acute coronary cases.10,11 Retrospective and prospective reports have noted a marked gender discrepancy in this condition.12,13 A recent review of published case series reveals that 90% of cases reported are in post-menopausal women.

The clinical presentation of TTC is often identical to acute myocardial infarction (AMI). Most patients with takotsubo cardiomyopathy present with typical anginal chest pain, dyspnea, ischemic changes on electrocardiogram (ECG), and elevated cardiac markers, where as syncope and out-of-hospital cardiac arrest are rare. Emotional stress, such as news of the death of a family member, divorce, or public speaking, is implicated as the trigger in approximately two-thirds of patients.\(^1\) However, other physical stressors such as non-cardiac surgery, sepsis, or critical illness have been reported.\(^2\) In one provocative prospective study, consecutive critically ill patients with no prior cardiac history who were admitted to a medical ICU underwent serial echocardiograms; 28% were noted to have transient reduced ejection fraction with imaging features consistent with takotsubo cardiomyopathy.\(^17\) Interestingly, there is a gender disparity in precipitants of TTC. In a recent TTC registry, Scheinder et al\(^12\) observed that physical stress was a more frequent trigger in men compared to women, 57% vs 30%; these results confirm previous reports in gender difference among hospitalized patients.\(^13\)

### Electrocardiographic changes and cardiac biomarkers

The most common abnormality on the ECG is ST elevation and T-wave inversion in the precordial leads.\(^18\) However there is significant variability in the frequency of these abnormalities in the literature. Prasad et al\(^1\) proposed two possible explanations for the variability. First, ST elevations are transient, thus the time from symptom onset to presentation might determine whether or not ST elevation is found. Secondly, there may be selection bias towards those patients with ST elevation, where early invasive coronary angiography and ventriculography are usually performed. Several investigators have proposed ECG criteria to discriminate TTC from acute myocardial infarction.\(^18\) The absence of Q waves, reciprocal changes, ST segment elevation in V1 with sum of ST elevation in V4-6 greater than that in V1-V3 as well as ST depressions in a VR have been shown to discriminate between the two diseases with high sensitivity and specificity.\(^18,19\)

Also, more extensive ST elevation in inferior leads were seen more frequently in TTC compared with anterior myocardial infarction.\(^20\) However, these findings were described in an Asian population and in a subsequent, larger study in Caucasian population, the discriminatory ability of these findings could not be validated.\(^21\) Hence, there may be some population differences in presenting signs and specific ECG changes should be considered suggestive but not diagnostic of TTC.

Evolutionary changes on ECG often occur two to three days after initial symptoms and presentation, with resolution of ST elevation, followed by diffuse and deep T-wave inversion, prolongation of QT interval. Pathologic q waves may be observed initially but rarely persist. T-wave inversion and QT-prolongation may persist for three to four months.\(^22\)

Modest elevation of cardiac biomarkers is often observed in TTC.\(^3,23\) In the systematic review of 14 studies which included 286 patients, 14% of patients had no measured troponin release.\(^11\) Also, cardiac troponin levels in TTC are much less than that typically observed in acute ST elevation myocardial infarction and are out of proportions to the extensive wall motion abnormalities and hemodynamic compromise.\(^25\) Troponin T levels are typically < 5ng/ml.\(^4\)

### Diagnosis

Due to the dramatic clinical presentation and high suspicion for acute myocardial infarction, most patients undergo emergent coronary angiography. Typical findings in TTC are normal epicardial coronaries, mild non-obstructive atherosclerosis, or rarely coexistent coronary artery disease.\(^1,2\)

Therefore, TTC is a diagnosis of exclusion which can only be made after coronary angiography. It should be on the differential diagnosis in any post-menopausal women over 50 years old presenting with chest pain and ischemic ECG changes particularly in the setting of emotional stress. Furthermore it should also be considered in critically ill patients with sudden hemodynamic compromise and/or heart failure. Researchers at Mayo Clinic proposed diagnostic criteria in 2004 [modified in 2008] for TTC which includes four components. (See Table 1).\(^1\)

### Cardiac imaging

Ventriculography reveals apical ballooning, with characteristic sparing of the basal segments and akinesis of the mid and apical left ventricle. However, variants of this pattern have been described including midventricular ballooning or basal and midventricular akinesis with apical sparing (inverted Takotsubo).\(^24\) In patients with typical TTC, the wall motion abnormality usually extends beyond the distribution of a single coronary artery.

Other imaging modalities are complementary in diagnosis of the condition, eliciting potential complications and in directing management. Echocardiography can detect and measure the degree of left ventricular outflow (LVOT) obstruction and associated systolic motion of the anterior mitral valve.
and significant mitral regurgitation. LVOT obstruction is reported to occur in 25% patients and can have a major impact on acute management. In patients with hemodynamic compromise and shock, inotropes would worsen this situation and betablockers and pure vasopressor pharmacologic or mechanical support may be needed. The typical findings on cardiac MRI include the absence of delayed gadolinium hyperenhancement. This is specific to TTC and can help differentiate it from myocarditis and acute myocardial infarction in which delayed hyperenhancement is present.

Pathophysiology
The pathophysiologic basis of TTC has not been conclusively determined but several mechanisms have been proposed. The underlying histopathological findings on myocardial biopsy include interstitial infiltrates of mononuclear lymphocytes and macrophages with fibrosis and contraction band necrosis; these findings are distinctly different than those of coagulation necrosis seen in typical atherosclerotic epicardial artery occlusion and myocardial infarction. Potential pathophysiologic mechanisms include: multivessel coronary artery spasm with resultant ischemia and stunning of the myocardium; aborted myocardial infarction of a long wrap around left anterior descending artery [LAD]; microvascular dysfunction and myocarditis; and most prominently, catecholamine overload.

In the early Japanese literature, Dote et al. in the review of their 5 cases, suggested that multivessel coronary spasm was the cause of the reversible cardiomyopathy. However, the inability of intracoronary ergometrine or acetylcholine to induce vasospasm in a majority of patients with TTC (28% of patients), and the lack of coronary spasm during cardiac catheterization in the majority of patients presenting with TTC, makes multivessel coronary spasm unlikely. A possibility of a spontaneously aborted myocardial infarction has been put forth in patients with a long wrap around left anterior descending artery [LAD]; microvascular dysfunction and myocarditis; and most prominently, catecholamine overload. Enhanced sympathetic activity appears to play a central role in the pathophysiology of takotsubo cardiomyopathy. The last and most plausible mechanism is a catecholamine-induced stunning of the myocardium and local cardiac sympathetic disruption. Similarly, increased sympathetic activity is also observed during acute cerebrovascular accidents and during the catecholamine-induced cardiomyopathy in patients with pheochromocytoma. Excessive levels of catecholamines have been observed in patients with takotsubo cardiomyopathy. Catecholamines have been shown to induce myocardial damage, and excessive stimulation of cardiac adrenergic receptors has led to transient LV dysfunction in animal models. Furthermore, a recent hypothesis favors local cardiac sympathetic disruption. Y-Hassan argues that the emerging evidence in animal models, showing local cardiac sympathetic nerve endings with local noradrenaline (NE) release and spillover to the myocardium, as well as the circular ventricular wall motion abnormality that follows the nerve end distribution rather than vascular distribution support the hypothesis of local sympathetic disruption as the pathologic mechanism underlying TTC.

Prognosis and Treatment
Takotsubo cardiomyopathy has an excellent prognosis, with full and early recovery in virtually all patients. The majority of patients have normalization of LVEF within a week and all patients by 4-8 weeks. The reported in-hospital mortality is low (0-8%) with the largest case series reporting 3% mortality, it may be increased in those with underlying conditions. Long-term survival is similar to the general population. In published data, the reported 4-year recurrence rate is approximately 4-10%. The mechanisms underlying recurrence or risk factors predisposing an individual patient to recurrence are not understood.

Although TTC has a favorable prognosis, several acute complications have been reported and should be anticipated. Congestive heart failure is documented in 3-46% of published cases, but hypotension and shock are rare in 4%. Systemic thromboembolism is reported in 5%. LVOT obstruction has been seen in 20-25% of patients but symptomatic obstruction is uncommon. Recent data suggest the arrhythmias, including atrial fibrillation, are presents in 10-26% of cases, but fatal arrhythmias such as ventricular fibrillation are rare.

Takotsubo cardiomyopathy is a temporary condition and hence the goals of treatment are usually conservative, supportive care. The therapy is guided by the patient’s clinical presentation and hemodynamic status. Despite the putative causal role of catecholamines in the disorder, patients who present in cardiogenic shock, and in the absence of LVOT obstruction, may be treated with inotropes. Alternatively patients may derive further benefit from mechanical hemodynamic support with intra-aortic balloon pump or rarely, left ventricular assist devices. If LVOT obstruction is present with cardiogenic shock, inotropes should be avoided and phenylphrine is the pressor agent of choice often combined with betablockade. Most experts advocate guideline-directed medical therapy for patients with left ventricular dysfunction. This includes cardioselective beta-blockers and ACE inhibitor for a short period of time (3-6 months). Full anticoagulation is usually reserved for those with documented ventricular thrombus or evidence of embolic events.
CONCLUSION

Takotsubo cardiomyopathy is an acquired, transient cardiomyopathy with an excellent prognosis. Patients present after an acute emotional or physical stressor with signs and symptoms similar to acute coronary syndrome but on coronary angiography do not have obstructive coronary artery disease. Catecholamine cardiotoxicity is the most likely causative mechanism. Typically, TTC has acute left ventricular systolic dysfunction sparing only the base of the heart and may be complicated by heart failure. Supportive treatment is the mainstay of therapy.

References


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ABSTRACT
Recent technological innovations in CT and MR imaging of the heart have vastly expanded the clinical utility of these modalities allowing them to complement and in some ways surpass the capabilities of more traditional methods. Cardiac MR (CMR) has an unrivaled ability to assess contractile function, characterize tissue, and detect minute areas of scar. In turn, CMR can reliably risk stratify ischemic heart disease and has emerged as a non-invasive gold standard technique for imaging non-ischemic cardiomyopathies.1 Cardiac CT (CCT) by comparison reveals cardiac structure and, in particular, coronary anatomy with remarkable sub-millimeter detail. For the first time, coronary stenoses can be directly and reliably visualized non-invasively. Owing to its very high negative predictive value for the detection of significant coronary obstruction, CCT can accurately exclude coronary disease as a cause of chest pain in low- to intermediate-risk populations. This article describes these modalities and their recent clinical advances.

KEYWORDS: Cardiac CT (CCT), Cardiac MR (CMR)

INTRODUCTION
This article briefly reviews the methodologies of CCT and CMR, their specific roles in the diagnosis of cardiac pathophysiology, and their utility in outcomes assessment and prognosis with various disease states.

Cardiac MR: The Basics
Magnetic resonance imaging is based on the absorption and subsequent emission of radiofrequency (RF) energy by water protons in various tissues of the body while immersed in a strong magnetic field. The RF emission is tissue dependent and leads to the unparalleled ability of MRI to distinguish subtle regional tissue differences within a single organ of the body, for example scar or edema within myocardium (Figures 1 and 2). With intravenous gadolinium-based contrast agents, MRI can further distinguish tissues based on their blood flow and blood volume differences. Using ECG-gating for stop-action imaging and novel acquisition methods, MRI can readily demonstrate regional myocardial differences in tissue perfusion and in the same examination detect areas of acute myocyte necrosis or scar – sometimes 1 cm³ or less. Myocardial fibrosis is a common endpoint of many cardiomyopathies, but the geographic patterns of fibrosis vary between disease states. As will be seen, with CMR these patterns commonly point towards a limited differential diagnosis, or in some cases the specific diagnosis. In the setting of ischemic heart disease, scar delineation has important prognostic utility. It has been shown that CMR with contrast accurately predicts viability – that is whether or not underperfused tissue will recover function after revascularization – and is probably the best method for determining this.2 Moreover, the presence of even a small amount of scar,

Figure 1. Short axis (a) bright-blood and (b) post-contrast CMR images from a patient with occlusion of the right coronary artery. A small (bright) inferior scar is demonstrated (arrows) consistent with an infarction. LV/RV: Left/Right ventricle.

Figure 2. Vertical long axis (a) dark blood and (b) post-contrast CMR images from a patient with acute myocarditis. Bright areas of myocardial edema in image (a) (arrows) overlap spatially with areas of acute myonecrosis in image (b) (arrowheads). LA/LV: Left atrium/ventricle.
much smaller than can be detected with nuclear methods, confers a substantial increase in the risk of major adverse cardiovascular events compared with no scar.3

Combining techniques for tissue characterization with cine movie loops having high spatial and high temporal resolution yields a robust evaluation of myocardial tissue and contractile function. Moreover, dynamic MR imaging during contrast infusion under conditions of induced coronary vasodilation [with intravenous adenosine for example] delineates regions of underperfusion due to upstream coronary artery stenosis. In its ability to detect significant coronary obstruction, CMR stress perfusion is superior to nuclear pharmacologic stress perfusion.4

Another powerful tool in the CMR arsenal is so-called phase-contrast MRI where image brightness is proportional to tissue velocity. Importantly, this technique permits dynamic quantification of blood flow (in cc/min) through large vessels enabling calculation of regurgitant valve severity and shunt fraction. As with echo, CMR can also characterize the severity of valvular stenosis.

The typical CMR study can be completed within 45 to 60 minutes. The patient is required to undergo a series of breath-holds while lying flat, which are generally well tolerated. The duration of the breath-holds is variable and can be adjusted based on the patient’s capability. Generally, the imaging of patients with arrhythmias is non-problematic, and MR imaging, like CT, is not significantly hampered by body habitus.

Advantages, disadvantages, and appropriate indications of CMR are listed in Tables 1 and 2.5

Cardiac CT: The Basics

CT is an x-ray based modality in which a ring, or gantry, containing an x-ray tube diametrically opposite a series of detectors rotates around a patient as the patient is moved through the ring. With modern scanners, volumetric data with submillimeter spatial resolution is collected over the scanned area of interest allowing images to be reconstructed in any orientation with equal clarity. Early CT systems lacked the spatial and temporal resolution to adequately visualize cardiac structures. The advent of very rapid gantry rotation, ECG-gating, and sub-mm resolution now permits stop-action imaging of very small rapidly moving structures such as the coronary arteries [Figure 3]. With intravenous iodinated contrast, CT readily depicts cardiac morphology and vascular anatomy and can be useful for...
unraveling congenital and acquired cardiovascular anomalies. While cardiac masses and thrombi are generally evident with CT, MRI is usually preferred for mass characterization because of its superior tissue contrast resolution.

Cardiac CT scans can be performed rapidly, with typical table times of ~10 minutes and actual scan times of less than 10 seconds. With current CT technology lower heart rates generally provide better scan quality, and patients are often given intravenous beta-blocker prior to the scan. Contrast and radiation are necessary elements of the study. The newest scanners and imaging protocols have decreased average patient radiation exposure, and doses are usually at or below those of nuclear myocardial perfusion imaging using $^{99m}$ Tc-sestamibi. In contrast to CMR, only a few breath holds are necessary with CCT.

Advantages, disadvantages, and appropriate indications of cardiac CT are listed in Tables 1 and 3.

Roles of CMR and CCT in Specific Cardiac Diseases

**Evaluation of Ischemic Heart Disease**

As the number one cause of death in the US, identification and qualification of coronary artery disease is a critical area for diagnostic evaluation. Diagnosis of acute plaque rupture in a coronary artery is typically made using a combination of history, electrocardiogram, and cardiac biomarkers, and risk-scoring systems help to predict which of these patients require urgent coronary angiography. In patients with acute coronary syndromes not indicated for emergent angiography, and those patients with progressive luminal narrowing, non-invasive imaging techniques are important tools for accurate diagnosis and further management decisions. Ideally, a comprehensive non-invasive diagnostic test is able to assess coronary anatomy and lumen defects, plaque composition, tissue perfusion, cardiac function as a result of stenosis, and viability of myocardium.

Most of these items can be met when patients with ischemic heart disease are evaluated using CMR. A large prospective study compared adenosine stress CMR with adenosine stress nuclear imaging (Single Photon Emission Computed Tomography, SPECT) in suspected ischemic coronary disease and found similar specificity for both modalities but a superiority in sensitivity, negative predictive value, and overall diagnostic accuracy for CMR. Cardiac function assessment using CMR is highly accurate and CMR is considered the reference standard for non-invasive assessment of chamber volumes and ventricular function.

**Table 3. Appropriate indications for CCT (Modified from Table 8 in Taylor et al. 6)**

<table>
<thead>
<tr>
<th>CHD: Coronary heart disease. Other abbreviations are in Table 2.</th>
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<tbody>
<tr>
<td><strong>Coronary angiography</strong></td>
</tr>
<tr>
<td>• Nonacute symptoms, possibly an ischemic equivalent</td>
</tr>
<tr>
<td>- Intermediate PTP of CAD and ECG interpretable and able to exercise</td>
</tr>
<tr>
<td>- Low/Intermediate PTP of CAD and either ECG uninterpretable or unable to exercise</td>
</tr>
<tr>
<td>• Acute chest pain</td>
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<tr>
<td>- Normal ECG and cardiac biomarkers and low/intermediate PTP of CAD</td>
</tr>
<tr>
<td>- Low/Intermediate PTP of CAD and ECG uninterpretable</td>
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<tr>
<td>- Low/Intermediate PTP of CAD and either nondiagnostic ECG or equivocal biomarkers</td>
</tr>
<tr>
<td>• New onset or newly diagnosed clinical heart failure to assess etiology</td>
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<tr>
<td>- Low/Intermediate PTP of CAD and reduced LV ejection fraction</td>
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<tr>
<td>• Intermediate preoperative coronary assessment prior to noncoronary cardiac surgery</td>
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<tr>
<td>• Continued symptoms after normal ECG exercise test</td>
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<td>• Intermediate risk findings on Duke Treadmill Score</td>
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<tr>
<td>• Discordant ECG exercise and imaging results or equivocal stress imaging results</td>
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<tr>
<td>• Evaluation of graft patency after coronary bypass in symptomatic patient</td>
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<tr>
<td>• Evaluation of left main stent patency in asymptomatic patient</td>
</tr>
<tr>
<td>• Calcium Score: Family history or premature CHD and low/intermediate PTP of CAD</td>
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<tr>
<td>OR asymptomatic with no known CAD and intermediate CHD risk estimate</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Congenital heart disease</strong></th>
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<tbody>
<tr>
<td><strong>Evaluation of LV function after acute MI or in HF patients in the setting of inadequate images from other noninvasive methods</strong></td>
</tr>
<tr>
<td><strong>Quantitative evaluation of right ventricular function/morphology (ARVC)</strong></td>
</tr>
<tr>
<td><strong>Evaluation of suspected dysfunctional native or prosthetic valves or of a cardiac mass in the setting of inadequate images from other noninvasive methods</strong></td>
</tr>
<tr>
<td><strong>Pericardial anatomy</strong></td>
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<tr>
<td><strong>Pulmonary vein mapping prior to ablation for atrial fibrillation</strong></td>
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<tr>
<td><strong>Coronary vein mapping prior to biventricular pacemaker placement</strong></td>
</tr>
<tr>
<td><strong>Localization of coronary bypass grafts and other retrosternal anatomy prior to reoperative chest or cardiac surgery</strong></td>
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</table>
As mentioned earlier, necrotic tissue and the corresponding wall-motion abnormalities can be accurately distinguished from viable tissue, despite regional functional defects, with contrast CMR.

The use of cardiac CT (CCT) in the detection of significant coronary artery disease relies on its excellent spatial resolution. CCT can accurately diagnose coronary stenoses >50%. Further, the high negative predictive value of this technique for detecting significant obstructive disease has permitted chest pain units to safely, efficiently, and cost-effectively 'rule out' coronary disease in low-intermediate risk populations. The spatial resolution of CT also lends itself to an assessment of coronary bypass grafts, large coronary stents (Figure 3), and congenital coronary anomalies. Registry data suggest that the presence of even non-obstructive atherosclerotic plaque confers increased risk of major adverse cardiovascular events.

While efforts to evaluate atherosclerotic plaque composition to determine likelihood of plaque rupture are not yet mature, coronary artery calcification is a definite marker of atherosclerosis. Coronary artery calcium (CAC) scoring using non-contrast CT technology is a well-established tool for risk assessment in asymptomatic patients, particularly those with intermediate pretest risk for coronary disease.

**Non-ischemic cardiomyopathies**

Diagnosis and characterization of non-ischemic cardiomyopathies has historically been difficult, sometimes requiring biopsy to make a definitive diagnosis. In most patients with new onset cardiomyopathy, it is important to first exclude ischemic heart disease, which both CCT and CMR can confidently do owing to their high negative predictive values. Further, cardiac MR can help delineate between the heterogeneous group of NICMs, and potentially give important information regarding prognosis.

Select cardiomyopathies are discussed below.

**Hypertrophic cardiomyopathy (HCM)**

In HCM, CMR like echo can identify regions of abnormal myocardial thickening. However, because CMR is a true 3-D modality with no 'blind spots' it occasionally reveals abnormalities not seen on echo. CMR has been able to detect an additional 6-12% of patients with HCM that were not found on echocardiogram. Moreover, CMR with contrast delineates fibrosis in a few typical patterns, further supporting and usually – with the support of morphologic data – cinching the diagnosis. Extent and severity of fibrosis may correlate with an increased risk of sudden cardiac death and in turn modify clinical management.

**Cardiac sarcoidosis (CS)**

Cardiac sarcoidosis is a challenging diagnosis that has traditionally relied on complex criteria issue by the Japanese Ministry of Health. Knowledge of cardiac involvement may prompt changes in clinical management. While cardiac involvement is clinically evident in only 5% of patients with sarcoidosis, post-mortem evaluation indicates that the prevalence is far greater. CMR has recently been shown to be superior to conventional criteria in identifying areas of myocardial damage due to sarcoid manifested as patchy enhancement in affected areas, typically in the subepicardial basal septum, in patients with the appropriate clinical context.

**Myocarditis**

Viral myocarditis can often have patchy midwall or subepicardial enhancement – typically in the inferolateral left ventricle or the septum – with extent and distribution of the enhancement associated with prognosis and probable viral pathogen.

**Figure 4.** (a) Short axis and (b) vertical long axis post-contrast CMR images of a patient with cardiac sarcoid demonstrate anterior and anteroseptal enhancement (arrows) consistent with myocardial damage.

**Figure 5.** Short axis (a) bright-blood and (b) post-contrast CMR images from a patient with dilated non-ischemic cardiomyopathy (DCM). (Coronary arteries were normal at catheterization.) Note the midwall stripe of enhancement in the septum typical for DCM.
Dilated Cardiomyopathy (DCM)
The vast majority of patients with DCM demonstrate no enhancement at CMR or a characteristic midwall stripe of enhancement in the septum (Figure 5).28 In patients presenting with heart failure, these findings aid in the distinction of DCM from ischemic heart disease where virtually all subjects demonstrate subendocardial or transmural scar when scar is present.

Cardiac Amyloidosis
Cardiac amyloidosis is an uncommon cardiomyopathy resulting from the deposition of amyloid protein in myocardial interstitium [as well as other tissues of the body]. Myocardial thickness is usually increased, and over time left ventricular function deteriorates. Diagnosis relies on endomyocardial biopsy, but may be inferred from positive fat pad biopsy in the appropriate clinical context. The CMR enhancement pattern for this condition is unique and very suggestive in unclear cases.29

Iron overload syndromes
In iron overload syndromes such as Thalessemia and sickle cell disease, CMR has the unique ability to detect myocardial iron deposition and quantify its severity.30 This advance has led to optimal detection of patients for chelation therapy prior to developing irreversible cardiomyopathy, significantly impacting mortality.

Valvular heart disease
The visual assessment of valvular heart disease by echo is generally superior to that of CMR and CCT. While CMR estimates of stenosis severity are reliable, CMR offers a unique advantage in its ability to quantify regurgitant fraction.31 Also, CMR is emerging as a useful tool for characterization of pulmonic valvular lesions often difficult to assess with echocardiography.

Pericardial disease
Although CT is able to demonstrate pericardial effusions, thickening, calcification and masses, CMR is generally regarded as the preferred modality for imaging the pericardium.32 A particular strength of CMR is its ability to distinguish constrictive pericarditis from restrictive cardiomyopathy, two entities with overlapping clinical presentations. In this regard, CMR is the gold standard.

Masses
Both intracardiac and extracardiac masses can be visualized using CMR and CCT, but again CMR is the preferred imaging modality. CMR assessment of a mass can be useful in evaluating its size, location, tissue characteristics including enhancement pattern, and functional significance. Recent studies have indicated that increased T2 signal, gadolinium enhancement, and lack of mobility all are suggestive of malignant neoplasm with reasonably high sensitivity and specificity compared with pathological correlates.33 CMR is accurate in the detection of intracardiac thrombus and is more sensitive than echo.34,35

Congenital Heart Disease
Evaluation of adult congenital heart disease by echocardiography can be hampered by limited views due to body habitus and low pre-test suspicion of a congenital anomaly. Both CCT and MRI are able to detect and characterize congenital cardiovascular lesions. Patients that have had previous surgeries can have a comprehensive anatomic evaluation using either of these techniques. In general, CCT is preferred when anatomy is the principle concern, for example in the detection and evaluation of congenital coronary anomalies.36 Cardiac MR offers the additional ability to quantify blood flow — for estimating shunt and valve lesion severity — and cardiac chamber volumes and ejection fraction, and characterize wall-motion abnormalities. Patients with stable congenital heart disease can be followed periodically using these non-invasive techniques to detect progression of pathology and support management decisions.

SUMMARY
Cardiac MR and CT have both become mature tools for the clinical evaluation of a vast array of cardiac diseases. These ‘new’ modalities are in many ways complementary to one another and to other tools in the traditional clinical armamentum and offer unique and powerful insights into cardiac pathology and pathophysiology. Their uses for diagnosing disease, predicting prognoses and outcomes, and modifying clinical management continue to emerge and evolve. CMR offers a dynamic range of capabilities for assessment of the cardiovascular system, allowing for a single, radiation-free imaging study to answer a multitude of clinical questions, especially with regards to cardiomyopathy. CCT has become an excellent non-invasive technique for anatomic assessment of the heart, and is a quick and useful tool for rapid evaluation of low-intermediate risk chest pain syndromes. The future is bright for CCT and CMR and for the physicians and patients who benefit from their use.

References


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New Diagnostic and Therapeutic Possibilities For Diastolic Heart Failure
EUY-MYOUNG JEONG, PhD; SAMUEL C. DUDLEY, JR., MD, PhD

ABSTRACT
Despite the fact that up to half of all heart failure occurs in patients without evidence of systolic cardiac dysfunction, there are no universally accepted diagnostic markers and no approved therapies for heart failure with preserved ejection fraction (HFpEF). HFpEF, otherwise known as diastolic heart failure, has nearly the same grim prognosis as systolic heart failure, and diastolic heart failure is increasing in incidence and prevalence. Major trials have shown that many of the treatments that are salutary in systolic heart failure have no beneficial effects in diastolic heart failure, suggesting different underlying mechanisms for these two disorders. Even criteria for diagnosis of HFpEF are still debated, and there is still no gold standard marker to detect diastolic dysfunction. Here, we will review some promising new insights into the pathogenesis of diastolic dysfunction that may lead to new diagnostic and therapeutic tools.

[Abbreviations: tetrahydrobiopterin, BH$_4$; cardiac magnetic resonance, CMR; diabetes mellitus, DM; heart failure with preserved ejection fraction, HFpEF; cardiac myosin binding protein C, MyBP-C; nitric oxide synthase, NOS]

KEYWORDS: heart failure, diastolic dysfunction, hypertension, diabetes, oxidative stress

INTRODUCTION
Heart failure is a major and growing public health problem in the United States affecting ~5 million patients in this country. Up to half of the 550,000 patients newly diagnosed with heart failure in each year have diastolic heart failure or heart failure with preserved ejection fraction (HFpEF). The disorder is the primary reason for 12 to 15 million office visits and 6.5 million hospital days each year. HFpEF is increasing in prevalence and incidence. Both systolic and diastolic heart failure has similar grim prognoses, and there are no approved therapies for diastolic heart failure.

What is diastolic dysfunction or diastolic heart failure?
Diastolic heart failure is a diagnosis of exclusion applied when a patient has heart failure symptoms, no evidence of other causes, and diastolic dysfunction. The disorder is thought to arise from impaired cardiac relaxation. While a considerable number of patients may have demonstrated diastolic dysfunction, a much smaller number suffer from heart failure. The determinants of progression from asymptomatic dysfunction to overt heart failure are unknown, and many people remain without clinical symptoms of heart failure. Another area of investigation is the role of diastolic dysfunction in right heart failure syndromes.

Symptoms
The major signs and symptoms of diastolic heart failure are lung congestion accompanied with breathlessness, coughing, tachypnea, dyspnea on exertion, or paroxysmal nocturnal dyspnea. Dyspnea on exertion is the sensation of difficult or uncomfortable breathing after a level of activity. Paroxysmal nocturnal dyspnea is a sensation of shortness of breath that awakens the patient, often after one or two hours of sleep and is usually relieved in the upright position.

Diagnosis
The incidence of diastolic dysfunction is increasing, affecting 15% percent of patients less than 50 years old and 50% of patients older than 70. Furthermore, there appears to be a gender bias towards women with approximately 75% patients with diastolic dysfunction being women. There are no specific blood markers of diastolic dysfunction, but there are some useful diagnostic tests.

Echocardiography
The fundamental requirements of the diagnosis are heart failure with a normal left ventricular ejection fraction (i.e. >50%). Suggestive of the diagnosis is the presence of left ventricular diastolic dysfunction. While the gold standard for diastolic dysfunction is thought to be derived from ventricular pressure volume loops, this is generally an impractical measure. Commonly, echocardiography can be used to evaluate the characteristics of diastolic left ventricular relaxation, filling, and distensibility. Echocardiography has been used to assess the dimensional changes and abnormal diastolic function by E/A ratio (i.e. early to late left ventricular blood filling velocity as measured by Doppler flow across the mitral valve in diastole). In early, mild diastolic dysfunction, impaired relaxation results in an inversion of the normal E/A ratio, increased mitral flow deceleration time, and increased isovolumic relaxation time, the time interval from closure of the aortic valve to onset of left ventricular filling.
In a second stage of diastolic dysfunction thought to be more severe, the pseudo-normal stage, the E/A ratio normalizes to E>A. Finally, patients can show a restrictive filling pattern with the E/A ratio >2. Aside from blood flow velocity across the mitral valve during diastole, direct assessment of mitral annular displacement can be used as a marker of diastolic function. Diastolic dysfunction is accompanied by significant reductions in tissue mitral annulus early longitudinal (E') velocities and the ratio of early annulus to late annulus (E'/A') velocities. Also, the ratio of early diastolic filling velocity to the early diastolic mitral annulus velocity (E/E') has been reported to have the highest correlation with invasive hemodynamic measures of diastolic dysfunction and can predict LV filling pressures (E/E' >15 suggests increased filling pressures). Color Doppler echocardiography can be used to estimate the rapidity of movement of a wave of blood across the mitral valve, and slow flow velocity is an indication for diastolic dysfunction.

**Echocardiographic speckle tracking**

Developing methods for diagnosis of diastolic dysfunction include assessing left ventricular relaxation directly. Speckle-tracking echocardiography is a new method that evaluates myocardial deformation. In this technique distinct echocardiography patterns, speckles, are followed to assess wall motion. Speckle analysis can be used to assess radial, longitudinal, and circumferential displacement and strain. Decreased strain rate in diastole is consistent with diastolic dysfunction.

**Cardiac magnetic resonance (CMR) imaging**

Recently, CMR imaging has been used to evaluate diastolic dysfunction. This technology provides the excellent spatial resolution, visualization of mitral valve inflow velocity, and pulmonary veins blood flows. With myocardial tagging (a pulse sequence that amounts to marking specific locations on the myocardium that can be followed in time), diastolic myocardial strain rate can be calculated. Delay and prolonged strain rates are related to relaxation impairment.

**MECHANISM AND THERAPEUTIC APPROACHES**

Research is shedding new light on the mechanism of diastolic dysfunction, and these new insights might lead to improved diagnostics and specific therapies. American Heart Association/American College of Cardiology guidelines recommend treatment of hypertension, maintenance of sinus rhythm, prevention of tachycardia, venous pressure reduction, and prevention of myocardial ischemia.

Epidemiological risk factors for diastolic dysfunction include age, hypertension, atrial fibrillation, and diabetes mellitus. Of note, diastolic dysfunction is observed in about 40% of patients with diabetes. These risk factors have considerable overlap with atherosclerosis, which suggested that these two conditions might have similar pathology. This idea was reinforced by the observation that β-blockers, angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs), and aldosterone antagonists, all salutary in systolic heart failure, have no beneficial effect in diastolic heart failure. These observations suggested that systolic and diastolic heart failure represent fundamentally different pathologies.

To begin to address the underlying pathology, we developed two unique mouse models of isolated diastolic dysfunction by inducing hypertension or glucose intolerance in the mice. Just like in blood vessels, nitric oxide made by nitric oxide synthase (NOS) is thought to contribute to cardiac relaxation. Hypertension-induced diastolic dysfunction was accompanied by cardiac tetrahydrobiopterin (BH$_4$; a co-factor in NOS) depletion, NOS dysfunction, a depression in myofilament cross-bridge kinetics, and S-glutathionylation of cardiac myosin binding protein C (MyBP-C), a cardiac contractile protein. This leads to impaired relaxation, and modified MyBP-C in the blood may represent a biomarker for diastolic dysfunction.

**Figure 1. A possible mechanism and marker for diastolic dysfunction.**

Hypertension and diabetes lead to cardiac oxidation and S-glutathionylation of cardiac myosin binding protein-C (MyBP-C), a cardiac contractile protein. This leads to impaired relaxation, and modified MyBP-C in the blood may represent a biomarker for diastolic dysfunction.
amelioretes diastolic dysfunction by reversing a decrease in cross-bridge turnover kinetics. These data provide evidence for modulation of cardiac relaxation by post-translational modification of myofilament proteins. In the same model, we found that ranolazine, a drug used now for angina, was able to ameliorate diastolic dysfunction. This effect was a result of ranolazine acting directly on the myofilaments. Recently, we have demonstrated a similar pathology occurs in a mouse model of type II diabetes mellitus, and a mitochondrial-target anti-oxidant is useful in reversing diastolic dysfunction. In this same study, glucose control alone was ineffective in reversing diastolic dysfunction. In preliminary studies, we have found that modified MyBP-C can be measured in blood and is elevated in patients with diastolic dysfunction [Figure 1].

Despite these promising observations, it appears that age-associated diastolic dysfunction may be a distinct pathology involving myocardial fibrosis. In a senescence-accelerated mouse model, diastolic dysfunction was accompanied by fibrosis that arose in conjunction with an increase in pro-fibrotic cytokines. This model suggests that there may be more than one form of diastolic dysfunction and that age-associated dysfunction would have distinctly different biological markers and treatments than hypertension or diabetes-associated diastolic dysfunction.

SUMMARY

In summary, diastolic heart failure occurs in approximately half of all heart failure cases. This type of heart failure is caused by a failure of the myocardium to relax properly. Cardiac diastolic dysfunction and subsequent heart failure appear to be distinct pathological entities from systolic heart failure. Diastolic dysfunction is accompanied by cardiac oxidation and oxidative modification of a cardiac contractile protein, MyBP-C [Figure 1]. Oxidation of this protein appears to result in increased sensitivity to calcium and delayed and incomplete relaxation. Treatments that inhibit oxidation such as BH4 and mitochondria-target antioxidants can treat diastolic dysfunction caused by hypertension or diabetes mellitus. Levels of modified MyBP-C may represent a new blood test for the presence of diastolic dysfunction and a marker of therapy. These observations suggest that physicians may be able to diagnose diastolic heart failure more accurately and dispense specific therapies in the future.

References


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Disclosures

Samuel C. Dudley, MD, PhD is the inventor on patent applications: 1) 11/895,883 Methods and Compositions for Treating Diastolic Dysfunction, 2) 13/503,812 Methods of Diagnosing Diastolic Dysfunction, 3) 13/597,622 Methods of Treating Diastolic Dysfunction and Related Conditions, 4) 13/658,943 Method of Improving Diastolic Dysfunction, 5) 13/841,843 Myosin Binding Protein-C for Use in Methods Relating to Diastolic Heart Failure, and 6) 61/728,302 Mitochondrial Antioxidants and Diabetes.

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Transcatheter Aortic Valve Replacement: A Review of Current Indications and Outcomes

WILLIAM PRABHU, MD; PAUL C. GORDON, MD

ABSTRACT
In patients with symptomatic severe aortic stenosis, surgical aortic valve replacement (SAVR) improves survival, quality of life, and functional status compared with medical therapy. Based on the results of the randomized PARTNER Trial, Transcatheter Aortic Valve Replacement (TAVR) using the Edwards Sapien balloon expandable valve is now available in the United States for patients who are either inoperable due to anatomic concerns or severe medical co-morbidities, or as an alternative in patients considered high risk for SAVR. Fifty-six patients have been treated with TAVR at Rhode Island Hospital from March 2012 through October 2013 with similar outcomes to The PARTNER Trial and several large European registries. Second-generation valves and lower profile delivery systems designed to reduce the incidence of vascular complications, stroke, and perivalvular leak, and extension of TAVR to intermediate risk surgical patients, are under investigation.

KEYWORDS: Aortic Stenosis, Transcather Aortic Valve Replacement

INTRODUCTION
When patients with severe calcific aortic stenosis (AS) develop symptoms, survival at 2 years is less than 50%, and by five years less than 10% of these patients are alive.1,2 Surgical aortic valve replacement (SAVR) improves symptoms, quality of life, and mortality.3 However, there are patients with severe AS with coexisting morbidities or anatomical concerns who have a prohibitive operative risk for SAVR. In the late 1980s, balloon aortic valvuloplasty was developed as an alternative to surgery, but this procedure did not improve mortality; it suffered from high restenosis rates, and thus remained a palliative treatment for inoperable patients.4 TAVR has been shown to improve mortality and relieve symptoms in patients deemed to have a prohibitive operative risk for SAVR compared to medical management.5 Since the first TAVR was performed in 2002, over 60,000 patients have been treated worldwide, either with a balloon expandable Edwards Sapien valve (Edwards Lifesciences Corp., Irvine, CA) or the self-expanding Medtronic CoreValve (Medtronic, Inc., Minneapolis, MN). Increased operator and institutional experience along with improved technology has led to procedural success rates greater than 95% with reduction in early mortality, vascular complications and stroke rates.

The PARTNER Trial
The PARTNER (Placement of Transcatheter Aortic Valves) Trial was the first, and to date, only randomized controlled trial of TAVR in patients with aortic stenosis. It thus remains a pivotal study guiding current practice. This was a two-armed trial in which patients with severe symptomatic aortic stenosis considered high risk for SAVR were randomized to either TAVR or SAVR (cohort A). If they were deemed inoperable (cohort B) by two cardiac surgeons and had adequate access for transfemoral TAVR, patients were randomized to TAVR or medical therapy.

Three hundred and fifty-eight patients were randomized in the inoperable arm of the trial (cohort B). Among those cohort B patients treated with TAVR, there was a 20.0% absolute reduction in mortality at 1 year compared with patients treated medically [30.7% vs. 50.7%, p<0.001], despite 85% of the medically treated patients receiving at least one balloon aortic valvuloplasty. Mortality continued to diverge with a 24.7% (43.3% vs. 68.0%) and 26.8% (54.1% vs. 80.9%) absolute reduction for the TAVR treated patients at years 2 and 3 [p<0.001], respectively. The number needed to treat was less than 4 patients to save one life. There were also significantly lower readmission rates for recurrent congestive heart failure (CHF), improved New York Heart Association functional class [75% vs. 42% NYHA class 1 or 2], and improved quality of life in TAVR treated patients.5,6 The very high mortality at 2 and 3 years in the medically treated patients in this contemporary trial confirms the poor prognosis for patients with symptomatic aortic stenosis, with no long-term symptomatic or mortality benefit from palliative balloon valvuloplasty.

Complications from TAVR included an increased risk of stroke in the TAVR-treated patients at 30 days (6.7% vs. 1.7%) and 2 years (13.8% vs. 5.5%), with the majority of early strokes occurring during the procedure from aortic atheroembolic or valvular particulate embolization. Due to the large diameter delivery sheaths [22 or 24 French requiring iliac artery diameter ≥ 7 or 8mm], major vascular complications were higher with TAVR [16.2% vs. 1.1%] as compared with medical therapy with or without balloon valvuloplasty.5,6
In cohort A of the trial, 688 high-risk operable patients were randomized 1:1 to either TAVR (transfemoral or transapical from a left thoracotomy if iliofemoral access was not adequate) or SAVR. Mortality was similar in each group at 30 days (TAVR 3.4% vs. SAVR 6.5%), 1 year (TAVR 24.2% vs. SAVR 26.8%), 2 years (TAVR 33.9% vs. SAVR 35%) and 3 years (TAVR 44.2% vs. SAVR 44.8%). Combined stroke or transient ischemic attacks were more frequent after TAVR than SAVR at 30 days (5.5% vs. 2.4%), 1 year (8.7% vs. 4.3%) and 2 years (11.2% vs. 6.5%). At 30 days, TAVR was associated with more frequent vascular complications (11.0% vs. 3.2%), but SAVR was associated with more frequent major bleeding (19.5% vs. 9.3%) and new onset atrial fibrillation (16.0% vs. 8.6%). More TAVR patients experienced early symptomatic improvement at 30 days, but by 1 year, symptoms and exercise tolerance were similar in both groups.7,8

Based largely on the results of the PARTNER Trial, the United States FDA first approved TAVR from a transfemoral approach using the Edwards balloon expandable Sapien Valve (Figure 1) in late November 2011 for patients deemed inoperable for SAVR, followed by approval of transfemoral or transapical TAVR as an alternative to SAVR in high-risk patients in October 2012. Since FDA approval of the Edwards Sapien heart valve two years ago, more than 13,500 patients in the United States have undergone TAVR. All patients treated with TAVR are enrolled in the Transcatheter Valve Registry. In a report of the first 7,710 patients (20% inoperable and 80% high risk, with 64% treated transfemorally), device success was 92% with a 30-day mortality of 5.5% and stroke rate of 2.0%.9

**PATIENT SCREENING**

The Valve Academic Research Consortium (VARC) has produced guidelines for effective implementation of TAVR across the United States.10,11 Patients with symptomatic aortic stenosis who are considered high risk for SAVR or inoperable are seen by a multidisciplinary team including at least two cardiac surgeons and an interventional cardiologist. The Society of Thoracic Surgery (STS) score is used to risk stratify patients for AVR; however, there are some comorbidities not accounted for in the STS score that prohibit SAVR. These include severe lung disease, severe liver disease with Child-Pugh B or greater cirrhosis, severe pulmonary hypertension with right ventricular dysfunction, and prior mediastinal radiation. Some frail and elderly patients may fail to pass a surgeon’s “eyeball test.” Anatomic considerations that carry a prohibitive surgical risk include severe kyphoscoliosis, a heavily calcified or “porcelain” ascending aorta, and one or more prior median sternotomies with dense adhesions, prior sternal wound infection, or bypass graft anatomy such as a left internal mammary graft coursing anteriorly under the sternum.

**Complications**

There are several serious procedural complications that may occur during TAVR. Patients may transiently develop shock and low cardiac output states following rapid pacing, required to prevent movement during valve deployment. This may require temporary hemodynamic support. Rarely, coronary artery obstruction may occur (1%-2%) – especially with low coronary ostia heights < 10mm, small coronary sinuses, or with bulky displaced native leaflet calcification.11 Annular rupture, aortic dissection, or valve embolization (< 1%) are rare, but may require pericardiotentesis or emergency median sternotomy with open surgical repair. Complete heart block requiring permanent pacemaker placement (especially with a preexisting right bundle branch block) occurred in 5-10% of patients.11

Vascular complications occur in approximately 10% of patients, including iliac artery dissection, perforation or avulsion.5,7,11 Most can be treated percutaneously with stents or stent grafts, but with proper procedural planning and vessel sizing, many vascular complications can be avoided. Major vascular complications are associated with an increase in late mortality.6,8

Perivalvular regurgitation occurs in nearly 85% of TAVR patients as a result of incomplete apposition of the valve prosthesis within the aortic annulus due to inadequate inflation and expansion of the prosthesis or calcific deposits that prevent proper seating. In the PARTNERS Trial, moderate or severe perivalvular aortic regurgitation was more frequent after TAVR compared with SAVR at 30 days and out to 2 years (6.9% vs. 0.9%). Any more than trivial perivalvular regurgitation is associated with an increased late mortality (hazard ratio 2.11, 95% CI 1.43-3.10), but it is uncertain if the aortic insufficiency itself is a cause of late mortality or just a marker of increased risk.6,8

Stroke occurs in 4%-8% of patients, with the majority occurring early due to aortic or valvular atheroemboli. The rate of stroke has fallen over time with improved procedural technique, improved delivery systems, and more aggressive

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**Figure 1.** (L) Edwards Sapien Valve, (R) Sapien Valve on balloon and Delivery System
anticoagulation. MRI-detected “silent” embolic events occur in nearly 85% of TAVR procedures. Embolic protection filter devices delivered from the radial artery to shield the aortic arch vessels are being tested in clinical trials.

RHODE ISLAND HOSPITAL OUTCOMES
From March 2012 through October 2013, 56 patients have undergone TAVR using the Edwards Sapien balloon expandable valve, 30 from a transfemoral approach and 26 from a transapical approach. During the same time period, 157 patients underwent SAVR and 89 patients underwent combined CABG and AVR for aortic stenosis (TAVR performed in 23% of the total AVR procedures). Procedural success has been 100%, with one annular perforation from displacement of bulky calcification that resulted in tamponade treated with pericardiocentesis. There have been 3 vascular complications in transfemoral TAVR patients (10%) from iliac artery dissections managed with stenting. We have had 2 major periprocedural strokes resulting in death at 34 and 60 days, and one minor stroke without residual neurologic deficit – an overall 5.4% stroke rate. Four patients died within 30 days (7.1% mortality), with 7 more deaths after 30 days for a total mortality of 20%. Of the first 14 patients with more than 1-year follow-up, 2 patients have died (14% mortality).

FUTURE DIRECTIONS
Next-generation lower profile valve and delivery systems are available and have replaced the first-generation Edwards Sapien valve outside of the United States. The Edwards Sapien XT balloon expandable valve (Edwards Lifesciences Corp., Irvine, CA) made of cobalt-chromium is delivered through an 18 or 19 French delivery system. In the PARTNER 2 Trial, 560 inoperable or extreme-risk patients with adequate iliofemoral access for TAVR were randomized to either the current FDA-approved Edwards Sapien valve or the lower profile Sapien XT valve. There was no difference in 1-year mortality (23.7% vs. 22.5%) or stroke (4.6% vs. 4.5%) between the devices. However, procedural times were shorter with Sapien XT, and major vascular complications were significantly reduced at 30 days (15.5% vs. 9.6%).

The Medtronic CoreValve is a self-expanding valve with bovine pericardial leaflets sewn to a nitinol cage that extends from the left ventricular outflow tract to the proximal ascending aorta (Figure 2). Four valve sizes range from 23-31 mm in diameter. This valve is used in approximately 50% of the TAVR procedures outside of the United States. The 18 French delivery system allows for transfemoral access through a minimum 6mm iliac artery. Multiple large registries using both the Edwards Sapien XT and Medtronic valves show procedural success is greater than 95%, with stroke rates reduced to 4-5% and vascular complications reduced to 5%. The need for permanent pacemaker is higher with the CoreValve (25.8%) compared with the Sapien XT valve (6.5%) due to extension of the self-expanding nitinol cage within the left ventricular outflow tract.

The 1-year outcomes for the CoreValve SURTAVI Trial (Surgical Placement and Transcatheter Aortic Valve Implantation) were recently released in October 2013. This was a non-randomized registry of extreme-risk patients with aortic stenosis (Society of Thoracic Surgery predicted combined morbidity and mortality > 50%). Four hundred and seventy-one patients were enrolled and treated with transfemoral TAVR using the CoreValve; 30-day mortality was 7.9%, with all cause mortality at 1 year of 24%. The 30-day stroke rate was 4.1%. While perivalvular leak was common, 80% of patients with a moderate or less perivalvular leak post procedure improved by 1 year. This was likely due to the self-expanding nature of this valve conforming to the aortic annulus over time.

TAVR has been extended to intermediate-risk patients in Europe with similar late 1- and 3-year mortality to SAVR in propensity-matched cohorts. Extension to intermediate-risk patients is being tested in the randomized PARTNER 2 and SURTAVI Trials. In PARTNER 2, operable patients are randomized to TAVR with the second-generation Sapien XT valve or SAVR. Patients with significant obstructive CAD are included in this trial (percutaneous intervention with TAVR vs. CABG and AVR). In the SURTAVI trial, intermediate-risk patients...
patients are randomized to TAVR with the CoreValve [femoral or direct aortic approach] or SAVR.

The direct transaortic retrograde approach from a small incision to the right of the upper sternum with a sheath placed in the ascending aorta is being developed as an alternative to the transapical approach in patients who are not candidates for transfemoral TAVR. In small-matched series, there were fewer bleeding complications compared with the transapical approach, and it may be a better alternative in patients with severe lung disease who may not tolerate a left thoracotomy. Within the PARTNER 2 trial, the direct aortic approach is being compared to transapical TAVR in a subset of patients.

With lower profile second-generation valves, some centers have been performing TAVR procedures in catheterization laboratories under conscious sedation without transesophageal echocardiography using percutaneous suture closure devices with excellent outcomes. This approach significantly lowers ancillary costs and hospital lengths of stay, with many patients being discharged 1 day post procedure. The PARTNER 3 trial is about to begin enrollment testing an even smaller diameter 14F delivery system with a third-generation balloon expandable valve with a self-sealing cuff to reduce the incidence of perivalvular leak.

SAVR remains the treatment of choice in most patients with severe symptomatic aortic stenosis. At present, TAVR remains an alternative to surgery in high-risk or inoperable patients. As technology improves to lower stroke rates, vascular complications, and perivalvular leak, TAVR likely will be extended to lower-risk patients with comparable outcomes to SAVR.

References

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