Case Study: “Not-So-Resistant” Hypertension

Ronald G. Victor, MD, and Mark K. Urman, MD

One in five hypertensive patients has drug-resistant hypertension. Defined as blood pressure (BP) that remains above goal values despite concurrent treatment with three antihypertensive drugs of different classes, resistant hypertension is the most common reason for referral to a hypertension specialist.

Multiple hypertensive mechanisms (neural, hormonal, vascular and renal) are often engaged simultaneously in resistant hypertensives. As a result, multi-drug regimens—three to five complementary agents—are almost always needed to achieve the recommended stretch BP goal of less than 130/80 mmHg. In many cases, hypertension specialists must also identify and address underlying conditions that are the source of high blood pressure, including chronic kidney disease (CKD), primary aldosteronism, obstructive sleep apnea and renovascular hypertension. Less common causes of secondary hypertension include pheochromocytoma, Cushing’s disease, hyperparathyroidism, aortic coarctation and intracranial tumors.

Only about 20 percent of the more than 50 million Americans with uncontrolled hypertension have truly drug-resistant hypertension. Most have pseudoresistance from improper BP measurement technique, white-coat reaction, medication non-adherence, ingestion of pressor substances or an inadequate BP regimen. Medication non-adherence explains half the cases of uncontrolled hypertension. In the following case study, we discuss a patient whose “resistant” hypertension was successfully addressed by revamping his regimen of BP medications.

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Cedars-Sinai Heart Institute
Eduardo Marbán, MD, PhD
Director
(310) 423-7557
Eduardo.Marban@csmc.edu

Approach to “Resistant” Hypertension

Causes of Pseudoresistance
- Measurement errors
- White-coat reaction
- Medication non-adherence
- Pressor substances
- Inadequate medical regimen

Causes of True Drug-Resistant Hypertension
- Secondary (identifiable) hypertension
- Severe primary hypertension (requiring countermeasures to all major hypertensive mechanisms: neural, hormonal, vascular and renal)

The most revolutionary advancement in three-dimensional (3D) echocardiography arrived in the past few years with the introduction of real-time 3D transesophageal echocardiography (TEE). Live 3D TEE is dramatically changing the way we evaluate patients—especially those with structural heart disease.

When studying 3D ultrasound imaging of blood vessels nearly two decades ago, we found the technology and its results were more intriguing than clinically useful. Low-resolution image quality, technical limitations and an extended processing time (about 24 hours for reconstruction of two-dimensional slices into 3D images), seriously restricted 3D echo’s practical value.

Today’s systems provide much quicker turnaround and higher-quality images, and 3D TEE is the subject of ongoing studies comparing its precision and utility in numerous applications to MRI and other established references. Results from our experience and other studies suggest that 3D TEE is an excellent tool in many situations, and the capabilities are growing as the technology continues to improve.

Compared to conventional two-dimensional echocardiography, 3D imaging provides better quantification of absolute cardiac chamber volumes, including left ventricular, right ventricular and left atrial volumes and their functions. It also offers improved visualization of the 3D structure and dynamic motion of the heart, especially heart valve structures.

Instead of producing cross-sectional images requiring mental reconstruction in three dimensions, the new technology creates images that can be manipulated and viewed in any plane desired, including “en face” views that can be especially useful in assessing and measuring the surfaces of valves and other structures. In the operating room, we can visualize the positions of heart structures and cardiac defects in actual relationship to each other in a surgical-anatomic view, which results in more effective communication between imaging specialists and surgeons.

### 3D TEE aids successful valve repair

3D TEE has been especially useful in guiding surgical repair of regurgitant aortic and mitral valves. The live 3D images allow the surgeon to precisely identify the anatomic abnormality and plan surgical reconstruction. This enhances the likelihood of successful valve repair and reduces the need for valve replacement. In one recent case, a 3D TEE image showed two ruptured chordae tendineae with prolapse and flail of the middle and medial posterior mitral leaflet scallops (Figure 1A). After surgical repair, diastolic and systolic views (1B and 1C) show the presence of a semicircular annuloplasty ring (even individual sutures can be identified), and the flail and prolapsing segments have been corrected. There was no residual mitral regurgitation.

Thanks to the very precise anatomic information provided by 3D TEE, the technology has also become an integral tool in a variety of percutaneous valve procedures, including several valve-related clinical trials: the EVEREST II trial of the Evolve MitraClip® for mitral valve repair (IRB #Pro00017803) and the PARTNER trial of the SAPIEN aortic valve device (IRB #12966). 3D TEE is useful for the guidance and positioning of catheters, as well as for the accurate measurement of valves and the precise localization of defects.

### Identifying structural abnormalities

The image quality, precision and maneuverability of 3D TEE provide a noninvasive imaging approach capable of detecting and characterizing structural abnormalities. In another case example, 3D TEE demonstrated the site, size, shape and morphologic characteristics of a left atrial myxoma (Figure 2A). Comparison of the live 3D TEE image and the surgical specimen corroborates the accuracy of the 3D imaging in regard to shape, size and morphologic appearance.
Applications for the treatment of heart failure

3D echo provides a robust assessment of regional timing to assist in the selection and monitoring of heart failure patients undergoing bi-ventricular pacing. It gives real-time information on valve functional dynamics and accurately depicts valve morphology and characteristics that are useful in treatment planning.

Conclusion

We have seen a steady increase in the use of live 3D TEE as this technology dramatically improves assessment of cardiac anatomy. This technology has become an indispensable tool in the cardiac noninvasive laboratory, cardiac surgical suite, and the cardiac catheterization laboratory for the assessment of structural cardiac defects or lesions, and the planning of interventional therapy.

Figure 2A: Surgical pathology specimen of the left atrial myxoma. 2B: Three-dimensional transesophageal echocardiography shows the myxoma within the left atrium attached to the fossa ovalis or intra-atrial septum (yellow arrow).

Robotic Technology Provides Less Invasive Procedure for Mitral Valve Repair

Alfredo Trento, MD, FACS

Approximately 40,000 patients a year in the United States, many under the age of 50, have mitral valve repair surgery, which involves delicate reconstruction of valve tissues. While traditional repair requires a midline sternotomy, robotic mitral valve repair is a less invasive procedure that includes only a few very small incisions on the right side of the right breast.

With the cutting-edge robotic technology now available, surgeons can actually macroscopically look directly at the mitral valve using high-resolution 3D imaging to gain a much better understanding of the valve's pathology compared to traditional sternotomy. During the procedure, miniaturized instruments are controlled by the surgeon's hand movements, which are scaled, filtered and translated into precise movements completed by four robotic arms located next to the operating table. The benefits of this minimally invasive approach over traditional surgery usually include reduced risk of infection, less blood loss, minimal scarring and faster post-hospital recovery. In general, a sternotomy results in a six- to 12-week recovery period, whereas with robotic mitral valve repair, patients can return to normal activities more quickly – often in only two weeks’ time.

To date, we have received positive patient feedback and good clinical results (comparable to the traditional sternotomy approach) from the more than 150 robotic mitral valve repair surgeries performed at Cedars-Sinai over the past four years.

In addition to mitral valve repair, robotic equipment can be used for ablation/Maze procedures, atrial septal defect repairs and defective tricuspid valve repairs. New indications include the removal of left ventricular tumors and left atrial tumors — and surgeons at Cedars-Sinai hope to soon begin using the system for coronary artery bypass surgery. Although robotic technology is currently being used for heart surgery at a limited number of institutions, thanks to its many benefits, we expect to see wider adoption as more surgeons receive training.
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Case example

A 45-year-old muscular obese gentleman (6’3”, BMI 39) was referred to the Cedars-Sinai Heart Institute for a second opinion on resistant hypertension of several years’ duration. Hypertension was initially detected when he presented to an emergency department at another hospital with a hypertensive urgency: BP of 224/151 mmHg associated with headache (stroke was ruled out). Both primary aldosteronism and pheochromocytoma were ruled out with formal hormonal testing and imaging studies. Obstructive sleep apnea was confirmed by polysomnography, but the patient could not tolerate continuous positive airway pressure (CPAP) therapy.

Treatment of the patient’s severe systolic/diastolic hypertension was initiated with verapamil, metoprolol and clonidine, with doses progressively maximized. Over the next year, amiloride, minoxidil, furosemide and guanfacine were added, but BP remained 160-180/110-120 mmHg.

When he presented to the Cedars-Sinai Heart Institute on this regimen, his BP was 170/120 mmHg. He was also taking ibuprofen daily for arthritis and headaches. His serum K+ had decreased from 4.0 to 3.4 and serum creatinine (SCr) had increased from 1.6 to 1.9. Plasma renin activity was <0.6 ng/ml/hr and serum aldosterone was 2.1 ng/dl.

All the above medications were gradually discontinued and replaced with the following: eplerenone 50 mg QD, hydrochlorothiazide 12.5 mg QD, carvedilol 12.5 mg BID and amlodipine 10 mg QD. The patient was advised to avoid NSAIDs as much as possible and referred to a sleep specialist, who found a CPAP apparatus and dose he could tolerate. The patient lost 30 pounds with diet and exercise but remains obese. On this new regimen, the patient’s office BP is 120-136/85-88 mmHg. SCr is 1.5 and serum K+ 4.5.

Discussion

The revised regimen removed several factors that often contribute to apparent drug-resistant hypertension, including NSAIDs, clonidine rebound and sub-optimal diuretic therapy. Minoxidil is a potent arterial vasodilator that we reserve for hypertension in patients with Stage 4 to 5 CKD until chronic hemoeldassemic can be initiated. Minoxidil requires combination therapy with a loop diuretic to counteract edema from volume retention and β-blockade to counteract reflex tachycardia. In this patient, neither minoxidil nor a loop diuretic was indicated because estimated glomerular filtration rate (GFR) was normal when the “elevated” SCr was considered in light of his very high BMI. Furthermore, renal autoregulation was preserved, as SCr did not rise (and actually fell) when BP improved markedly on the new regimen.

Standard β-blockers such as metoprolol, though strong antianginals, are weak antihypertensives and no longer considered first- or second-line therapy for uncomplicated hypertension. They are less effective than other agents in reducing central aortic BP and offer little if any protection against stroke. By comparison, carvedilol and other β-β-blockers are much stronger antihypertensives and thus more effective for resistant hypertension. Of the calcium channel blockers (CCBs), verapamil is a weaker antihypertensive than dihydropyridines such as amlodipine. Most patients with moderate or severe hypertension can be controlled with combination therapy that includes a RAS inhibitor, a dihydropyridine CCB and a low-dose thiazide. In the absence of an identifiable cause, a mineralocorticoid receptor antagonist and an α-β-blocker are recommended as highly effective fourth- and fifth-line therapy.

As illustrated by this case, a mineralocorticoid receptor blocker can be remarkably effective as add-on therapy for resistant hypertension – even when serum aldosterone is within the normal range. Eplerenone avoids the sexual side effects of spironolactone. It is also less potent: 50 to 100 mg of eplerenone causes a similar reduction in BP as 25 to 50 mg of spironolactone. Serum K+ needs to be monitored carefully to avoid hyperkalemia, especially when eplerenone or spironolactone is used in combination with a renin-angiotensin system (RAS) inhibitor or if the patient has CKD.

Eplerenone and carvedilol may be particularly effective in this patient because both aldosterone and norepinephrine contribute to hypertension in obstructive sleep apnea. CPAP often causes a small fall in BP but a large fall in transthoracic pressure, thereby reducing left ventricular afterload (the hemodynamic stimulus to pressure-overload hypertrophy) and atrial stretch (the hemodynamic stimulus to atrial fibrillation). Weight loss often improves insulin sensitivity more than BP.

The patient tolerated all medications well. He has been instructed in the use of a home BP monitor, and a renin-angiotensin system inhibitor will be added if home BP is above 130/80 mmHg.

Dr. Victor (left) is Associate Director for Clinical Research and Director of the Hypertension Center at the Cedars-Sinai Heart Institute, and is a Professor of Medicine at Cedars-Sinai. Dr. Urman (right) is Co-Director of the Preventive and Consultative Heart Center at the Cedars-Sinai Heart Institute.

Ronald.Victor@cshs.org, Mark.Urman@cshs.org