Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: January 31, 2023

Citation: Brandon L., Connolly N., et al., 2023. Cardiovascular Autonomic Dysfunction and its association with Aortic Stenosis. Medical Research Archives, [online] 11(1). https://doi.org/10.18103/mra.v11i1.3495

DOI: https://doi.org/10.18103/mra.v11i1.3495

ISSN: 2375-1924

REVIEW ARTICLE

Cardiovascular Autonomic Dysfunction and its association with Aortic Stenosis

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Abstract

Aortic stenosis remains the most common valvular abnormality that requires intervention and is becoming more prevalent with an ageing population. Untreated symptomatic severe aortic stenosis is associated with a mortality of 50-60% within two years. Valve replacement either surgical or transcatheter remains the only effective treatment.

The autonomic nervous system involuntarily controls many basic cardiac, respiratory, gastrointestinal and genitourinary functions and plays a central role in the regulation of heart rate and blood pressure. Cardiovascular autonomic dysfunction has shown to be a marker of increased mortality. We discuss current methods to assess autonomic function, alongside abnormalities noted in common cardiac conditions and their correlation to mortality, and review current literature available that confirms severe aortic stenosis is associated with dysregulation of cardiovascular autonomic system.

Aortic stenosis

Aortic stenosis (AS) is the second most common valvular abnormality and the most common requiring intervention. Incidence increases with age, being present in up to 2% of 60-year-olds and up to 10% of 80-year-olds[1,2]. This poses the challenge of successful and safe treatment of an elderly population.

The aortic valve is most commonly a trileaflet structure (also regularly referred to as tricuspid), or bileaflet in 0.5-2% of the population[3]. Unileaflet and quadrileaflet variants have been described. The leaflets are named according to proximity to a coronary artery, specifically the right coronary leaflet, left coronary leaflet, and the non-coronary leaflet. The valve is located between the left ventricular outflow tract (LVOT) and aortic root thereby dividing the high pressure ventriculo-arterial junction.

The aortic valve opens and closes up to 100,000 times per day, so is uniquely exposed to long term stresses. Aortic stenosis is an active disease process of fibrocalcification that results in orifice narrowing and LV outflow obstruction[3,4]. This in turn results in increased left ventricular (LV) pressure, compensatory LV hypertrophy (LVH) and diminished cardiac output (CO)[5]. Symptoms are described by the "classic triad" of shortness of breath, chest pain and syncope. Previously considered a "degenerative process" that could not be modified, recent histological assessments show AS is an active pathology of oxidised lipids and infiltrating inflammatory cells, perhaps opening pathways to possible therapies in the future[3,4,6]. Currently, no medications have been shown to slow or pause the disease process. Trials of statins, bisphosphonates and denosumab[7,8]. have not shown benefit, though research in ongoing with some hope PCSK-9 inhibitors may slow progression of AS following sub-analysis of the FOURNIER trial[9].

Risk factors for AS mirror those for coronary atherosclerosis, and include age, being male, hypertension (HTN), chronic kidney disease, hypercholesterolaemia, smoking, diabetes mellitus (DM) and established vascular disease[1,2]. Valvular specific risk factors include congenitally abnormal leaflets such as bileaflet valves (BAV) or previous rheumatic heart disease. Shear stress is particularly relevant to abnormal leaflets and patients with BAV typically develop severe AS earlier than those with trileaflet valves[10,11].

Aortic stenosis is usually diagnosed clinically and confirmed by transthoracic echocardiogram (TTE). Echo findings in severe AS include restricted movement of calcified leaflets, a transvalvular velocity > 4m/s, mean pressure gradient of > 40mmHg, an aortic valve area < 1cm2 and a dimensionless index of <25. Related parameters include LV ejection fraction (LVEF), degree of aortic regurgitation, assessment of other valvular abnormalities and measurement of right heart pressures. Low flow low gradient AS occurs when the valve gradients are disproportionate to valve area and may be more accurately determined by exercise or dobutamine stress echocardiography to distinguish severe versus pseudo-severe AS. Aortic valve area

does not increase in true severe AS with increased cardiac output. Cardiac CT can elucidate severity in uncertain cases. A calcium score of >2,000 for men and >1,200 for women indicates a high likelihood of severe AS[12].

Untreated symptomatic severe AS has a two-year mortality of up to 50%[13]. Previously, guidelines recommended active surveillance for patients with asymptomatic severe AS. However symptoms can be subjective and patients often have medical co-morbidities that cloud assessment e.g. chronic obstructive pulmonary disease and dyspnoea. This makes accurate and safe timing for such patients challenging. Ongoing studies are attempting to identify patients with AS at higher risk for whom surveillance may not be appropriate, despite not being overtly symptomatic. Some high-risk parameters are already included in treatment guidelines, such as depressed LVEF, very high gradient AS (> 5m/s), rapidly increasing gradient (> 0.3m/s per year), abnormal blood pressure response to exercise stress testing, or unexplained elevation of brain natriuretic peptide (BNP) levels[12]. Others warrant ongoing clinical studies and include the degree of LVH, left atrial size, LV strain patterns on TTE, autonomic parameters and abnormal biomarker levels such as troponin, fetuin-A, and copeptin[14,15 16,17].

Treatment options for severe AS are currently limited to valve replacement either surgically or transcatheter, and although effective, they do expose the patient to significant procedural risk. Valve replacement with mechanical valve necessitates long-term anticoagulation while bioprosthetic valves are at risk of degeneration over time.

The Autonomic Nervous System

The autonomic nervous system (ANS) consists of the sympathetic (SNS), parasympathetic (PNS) and enteric nervous systems (ENS). The SNS and PSN function without conscious control and are often considered to have opposing actions; "Fight or flight" for SNS, and "rest and digest" for PNS. They control many basic functions of the cardiac, respiratory, gastrointestinal (GI) and genitourinary systems.

From a cardiac perspective the ANS plays a central role in heart rate (HR) and blood pressure (BP) regulation and is tightly controlled to ensure appropriate hemodynamic response to potential fluctuations such as positional changes, exertion and volume status. This involves a rapidly responsive reflex arc that incorporates brainstem, spinal cord, efferent and afferent SNS and PNS nerve fibres, alongside baroreceptor and chemoreceptor input.

SNS and PNS nerves mostly consist of a two-neuron chain, one that synapses in local ganglions (the pre-ganglion nerve fibre) and one that innervates the target organ (the post-ganglion nerve fibre). SNS pre-ganglions are predominantly short and paravertebral, while PNS pre-ganglions are longer, synapsing nearer the end organ.

SNS pre-ganglion nerves secrete acetylcholine, and post-ganglion nerves secrete norepinephrine (NE) that acts on

alpha-1, alpha-2, beta-1, beta-2 or beta-3 adrenoreceptors, depending on the target organ. There are usually 3 cervical, 12 thoracic, 4 lumbar and 5 sacral paravertebral ganglions, that contain both efferent and afferent fibres thereby connecting the central nervous system to the peripheral[21,22]. The SNS in involved in increasing heart rate and blood pressure, increasing respiration via bronchiole dilatation, causing sweating and pupillary dilatation, and inhibiting urinary and GI function.

Efferent cardiac SNS innervation comes from the superior, middle and inferior cervical ganglions to form the superior, middle and inferior cardiac nerves, and T1-3/4 ganglions, with beta-1 receptors located on the surface of the heart at the sinoatrial node (SAN), atrioventricular node (AVN) and cardiomyocytes[23]. Binding of NE causes an increase in cyclic adenosine monophosphate (cAMP) in myocardial cells that results in an increase in chronotrophy, inotrophy, lusitrophy and dromotrophy[24]. Neurons also co-release neuropeptides such as neuropeptide Y, substance P, galanin and adenosine triphosphate (ATP) to augment SNS activity. Afferent sympathetic fibres return information to the brainstem, the nucleus tractus solitarus is the primary relay station for cardiovascular and cardiopulmonary reflexes[25]. Cardiac afferents also initiate local inflammatory and vascular reactions that may play a role in cardiac remodelling and transduce neuropeptides such as substance P, bradykinin and calcitonin gene-related peptide[26].

The PNS is comprised of cranial nerves (CN) III, VII, IX and X in addition to fibres that exit from the S2-S4 nerve roots and controls impulses to viscera in the pelvic cavity. Seventy-five percent of PNS function comes from CN X, the vagus nerve, which innervates most of the thoracic and abdominal viscera. The PNS supply to the heart from the vagus nerve is primarily mediated by M2 receptors that are expressed in abundance in nodal and atrial tissue, but sparsely in the ventricles. Acetylcholine binds to M2 receptors and decreases cAMP levels in myocardial cells, which slows conduction velocity through the AVN and slows the rate of depolarisation. This causes negative chronotropic and dromotrophic effects. It also reduces contractility of atrial cardiomyocytes, thereby reducing the "atrial kick" contribution to cardiac output[25,27,28]. Neuropeptides such as vasoactive intestinal polypeptide and nitric oxide may also be co-released from parasympathetic terminals[29].

The intrinsic cardiac nervous system (ICNS) describes the network of nerve fibres within the heart itself. Clusters are found in epicardial fat that are referred to as intracardiac ganglionated plexi and these operate together as local integration centres[30]. The ICNS is well described and can be subdivided into seven epicardic subplexuses: the dorsal right atrial (DRA), ventral right atrial (VRA), left dorsal (LD), ventral left atrial (VLA), middle dorsal (MD), right coronary (RC) and left coronary (LC) plexuses. Though significant anatomical variations exist, each ganglion contains afferent and efferent ANS input alongside

local neuron circuits with interconnecting neurons that are believed to have some independent neuronal activity[31].

Blood pressure control is a complex interplay between the ANS, baroreceptors, chemoreceptors, and the renin-angiotensin system.

Baroreceptors are spray type nerve endings that function as mechanoreceptors, are found in abundance at the carotid sinus and aortic arch, and in atrial tissue where they are often referred to as cardiopulmonary receptors. Baroreceptors are sensitive to changes in pressure, and function to tightly regulate and prevent large fluctuations in blood pressure on a rapid response basis. Essential hypertension leads to baroreceptor adaptation and resetting that maintains elevated blood pressure as the new normal target[32].

When distended afferent fibres send information to the rostral ventrolateral medulla of brainstem, which in turn causes sympathetic inhibition and parasympathetic activation that in turn mediates vasodilation, and negative chronotropic and inotropic effects. When baroreceptors sense a drop in pressure, they reduce afferent firing signals which has the opposite effects. This activates the SNS, increases total peripheral vascular resistance, cardiac output, and vagal inhibition.

Chemoreceptors are sensory organs that detect change in the chemical composition of blood, particularly of oxygen and carbon dioxide. Chemoreceptors are peripherally located in the carotid bodies and aortic arch and centrally in the medulla. Peripherally they detect change in the arterial partial pressure of oxygen, and relay information via the carotid sinus nerve to the brainstem. The resulting chemoreflex is a potent rapid mediator of blood pressure.

The renin-angiotensin-aldosterone system (RAAS) is a well described hormonal mediated system that plays a vital role in the slower regulation of blood pressure, alongside sodium levels and extracellular volume, and has much interaction with the ANS. Beta-1 autonomic receptors (ARs) on the kidney stimulate renin release, while angiotensin-II (Ang-II) receptors are present at synapses throughout the SNS. Ang-II binding enhances SNS neurotransmission by stimulating presynaptic release of norepinephrine from sympathetic nerves, inhibiting NE reuptake in nerve terminals and enhancing vasoconstrictor responses to NE[33] .

Autonomic dysfunction

Autonomic dysfunction can occur as an intrinsic or extrinsic disease process.
Intrinsic disease occurs when a primary pathology directly damages nerve fibres e.g. primary autonomic failure, Parkinson's disease, Multiple system atrophy (MSA), diabetes mellitus (DM) or amyloid. Extrinsic autonomic dysfunction results when secondary changes result from other diseases processes e.g. myocardial infarction, heart failure (HF) or stroke[34–36]. This affects ANS function and regulation and results in excess adrenergic activation. SNS overactivation leads to excess neurohormonal activity with

recruitment of the RAAS system, production and activation of inflammatory cytokines, and catecholamine excess, which can result in ventricular arrhythmia, HF and sudden cardiac death[27,37]. Symptoms related to autonomic failure are broad and can include lightheadedness and syncope from cerebral hypoperfusion on standing, gastroparesis, constipation, sweating abnormalities and sexual dysfunction.

Assessing Autonomic function

Autonomic function is difficult to measure directly and assessment mostly relies on surrogate markers. These include cardiovascular reflexes determined by provocative tests such as Ewings reflex tests, baroreflex sensitivity (BRS) and head up tilt table testing (HUT), heart rate measurements, imaging measurements of norepinephrine uptake, plasma levels of NE, and sudomotor tests. Often a variety of methods are used collectively given the complexity of the ANS.

Ewings tests comprises five measurements, three of which assess parasympathetic function and two which assess sympathetic function. Heart rate responses to deep breathing (Expiration/Inspiration ratio), to standing (30s/15s ratio), and to the Valsalva manoeuvre (Valsalva ratio) reflect parasympathetic function, and blood pressure responses lying to standing and to a sustained handgrip reflect sympathetic function. Each of these tests are assigned a score, 0 for normal, 0.5 for borderline, and 1 for abnormal, and the sum of the scores make up the Ewing score[38]. Measurement can be cumbersome and limited by patient factors in the elderly such as difficulty completing a Valsalva manoeuvre, arthritis or mobility issues.

Heart rate parameters also reflect autonomic function and a number of analyses are established measures. The most common and widely studied heart rate variability (HRV). This involves determination of RR intervals that are not constant but fluctuate around a mean value and reflect complex interaction between the SNS and PNS. HRV is measured via time-domain or frequency-domain analyses[39].

Time domain assessments include:

- SDNN - the standard deviation of NN, so-called normal-to-normal intervals. It encompasses both long- and short-term variability and thus describes overall HRV.
- SDANN - the standard deviation of the average NN intervals is calculated over successive 5-min periods of 24-h recording. It evaluates slow changing components of HRV.
- rMSDD - the square root of the mean squared differences of successive NN intervals. It describes short-term variation and thus reflects parasympathetic activity.
- pNN50 - the proportion of differences in consecutive NN intervals that are longer than 50 ms is similar to rMSDD.

Frequency domain analyses measure the frequency and magnitude of the cyclical nature in changing RR intervals and thus allow division into high frequency, low frequency

and very low frequency domains. High frequency (HF) is thought to represent the very fine variability seen with respiration at rest, mainly PNS mediated, and low frequency (LF) reflects a mix of SNS and PNS activity. Measurements are carried out over 5 minutes and most studies report results using levels of HF (0.15-0.4Hz), LF (0.04-0.15Hz) and a ratio of LF/HF.

Other heart rate (HR) parameter assessments include heart rate turbulence (HRT) which describes heart rate change seen after a PVC, and heart rate recovery time (HRRT) that reflects how quickly the HR returns to baseline after exercise or an orthostatic challenge. Early heart rate recovery indicates intact PNS function. HRRT after orthostatic challenge correlates with CV disease and mortality. Furthermore, velocity of HRR between 10 and 20 seconds predicts all-cause mortality[40].

Baroreceptor sensitivity techniques assess responsiveness of the carotid and aortic arch baroreceptors following an infusion of phenylephrine. HR and BP response are measured in a beat-to-beat fashion. A depressed response indicates poor prognosis[41].

Cardiac sympathetic imaging techniques use radiotracers to functionally evaluate postganglionic presynaptic cardiac sympathetic innervation. Common tracers are meta-iodobenzylguanidine (MIBG), or ^{11}C-hydroxyephedrine which requires positive emission tomography. When NE is released at the synapse in myocardium it binds to the beta 1-adrenoreceptor on the postsynaptic membrane. MIBG, an analogue of NE, is reabsorbed into the presynaptic membrane and accumulates in the nerve ending vesicles[42–44]. Impairment of the NE-1 reuptake is reflected by impaired uptake of MIBG. Measurements taken include early and late phase heart mediastinum ratio (H/M), and washout rate (WR). Lower H/M ratios and higher WR indicate abnormal SNS function.

Direct measurement of muscle sympathetic nerve activity (MSNA) can be achieved by microneurography. A tungsten microelectrode is placed invasively to measure postganglionic vasoconstrictor activity most commonly along the peroneal nerve as it passes through the anterior tibialis muscle. Nerve discharges are amplified, filtered and stored. Most publications report burst frequency/min or burst per 100 heart beats. MSNA is deranged in all subtypes of heart failure and abnormality is an independent predictor of mortality. MSNA improves with exercise programmes, beta blockade and cardiac resynchronisation therapy[45,46].

Plasma and urine levels of norepinephrine as surrogate markers of SNS overactivity. However, only 20% of NE spills over from the synapse to the circulation and only 2% exits via the urine thus removal can be affected by poor renal clearance or reduced cardiac output and thus levels may not fully reflect SNS activity[47].

Sudomotor tests can also be done to test autonomic control of thermoregulation, the most precise being Quantitative Sudomotor Axon Reflex Test (QSART).

Cardiac Autonomic Dysfunction

Cardiac autonomic dysfunction (CAD) is a term used frequently for the autonomic abnormalities seen in patients with DM and remains an ongoing area of active research that is estimated to affect anywhere between 1-91% of patients with type 1 diabetes mellitus (T1DM) patients, and 25-75% of patient with type 2 diabetes mellitus (T2DM)[48,49]. CAD impacts patient's quality of life and is a marker of higher mortality[50,51]. It most likely results from hyperglycaemia related oxidative stress and mitochondrial dysfunction causing neuronal dysfunction and death, and affects long nerves first i.e. the vagus nerve[52]. Loss of vagal control on the heart leads to unopposed sympathetic drive and tachycardia. As CAD progresses, it can lead to sympathetic denervation of the heart, symptoms of orthostasis, blunted heart rate response to physical stressors, exercise intolerance and silent myocardial infarction. Improved glycaemic control has been shown to slow development and progression of CAD[53].

Autonomic Dysfunction and Cardiac Conditions

The relationship between heart failure (HF) and autonomic dysfunction is increasingly studied and ANS modulation by medications in HF has been shown to improve mortality[54]. ANS is initially works to increase cardiac output but ultimately results in excess activation and long-term maladaptive effects, rather than direct nerve injury. The majority of data comes from studies of Heart failure with reduced ejection fraction (HFrEF). Initially, there is increased release and decreased reuptake and breakdown of NE, which increases cardiac contractility and HR and thereby CO. Increased sympathetic tone increases vasoconstriction, MAP, and activates the RAAS neurohormonal system[55,56]. Though useful in the short term this ultimately becomes maladaptive. Excess fluid retention increases stroke volume which in the long-term increases end-diastolic pressure, stiffness, and impairs ventricular filling.

HFrEF treatment targets that these areas of dysregulation improve mortality. Beta blockers modulate the SNS[57–59], and angiotensin-convertase enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs) and mineralocorticoid receptor antagonists (MRAs) target RAAS[60–62]. The SHIFT trial assessed the addition of ivabradine (a heart rate controlling agent) to HF management and showed improved mortality with better heart rate control[63].

Invasive modulation of the ANS

Invasive attempts to control resistant HTN by modulating the SNS include renal artery denervation (RDN) and carotid baroreceptor activation therapy (BAT). RDN is based on the anatomical and physiological observation that afferent and efferent sympathetic nerves to the kidneys run in close proximity to the renal arteries. Induction of efferent nerve damage reduces renal vasoconstriction, renin production and sodium and water retention[64]. Early studies indicated sustained BP reduction in treatment resistant patients, however a

sham-controlled randomised controlled trial that delivering single point radiofrequency ablation (RFA) to the renal artery was disappointing[65].

Carotid baroreceptor activation therapy (BAT) is another invasive method developed to control BP in treatment resistant patients, recognising the role the baroreflex plays in day-to-day BP regulation. The Rheos-Pivotal trial, a double-blind, randomized, prospective, multicenter, placebo-controlled Phase III clinical trial, showed a higher proportion of patients achieving a systolic BP <140 but noted a 25.5% adverse event rate[66].

A second-generation unilateral electrode device was developed based on Rheos trial observations that unilateral stimulation produced similar BP drops, with reduced implant time and complication rates, and improved battery life[67]. The device was subsequently trialled in HF patients, with the hope that reducing sympathetic drive would reduce production of stress-related hormones, reduce renin production and increase diuresis. In the BeAT-HF trial BAT significantly improved functional status, quality of life, and exercise capacity in patients with an LVEF <35%[68].

Ventricular arrhythmias and ANS

The ANS and particularly sympathetic drive has long been recognised as a contributor to cardiac arrhythmia. Cardiomyocytes contract with excitation-contraction coupling, where the pacemaker cells of the heart depolarise spontaneously (SAN, AVN, purkinje fibres), and the action potential spreads rapidly to the non-pacemaker cardiomyocytes. Anti-arrhythmic medications target various pathway components[69].

The inflow of calcium to the myocyte triggers calcium release from the sarcoplasmic reticulum (SR), which binds to troponin-C and allows actin and myosin interaction, with subsequent contraction. Strength of contraction is increased by higher calcium levels and stretch on the myocyte via the Frank-Starling mechanism. Cardiac contraction is highly oxygen dependent[69]. Contraction and relaxation are both active ATP-dependent processes[70].

Binding of NE to beta-1 adrenoreceptors in myocytes enhances calcium entry into the cell. Catecholamines also increase the rate of re-uptake of calcium into the SR, thus aiding relaxation. These actions shorten the action potential and refractory period, increase dispersion of repolarisation in the ventricles, enhance conduction through the AVN and increases T-peak to T-end on electrocardiography (ECG). This increases risk of ventricular arrhythmia, particularly with a vulnerable substrate such as acute ischaemia or heart failure[71–73]. Excess activation of the RAAS alongside sympathetic excess in HF patients further predisposes to ventricular arrhythmia[74–76].

Cardiac sympathetic denervation (CSD) can reduce ventricular arrhythmias and may be achieved temporarily by left stellate ganglion block or more permanently with an open procedure where left or bilateral CSD is undertaken. This is mostly undertaken in

patients suffering from ventricular electrical storm[77,78].

Autonomic function and aortic stenosis

Aortic stenosis significantly alters cardiac haemodynamics. Progressive narrowing of the outflow orifice creates high outflow resistance, causing a large pressure gradient to occur across the aortic valve as LV peak systolic pressure increases to maintain outflow. This leads to increased LV wall stress (afterload) which increases end-systolic and end-diastolic volumes and activates the Frank-Starling mechanism. In the longer term these mechanisms cause myocyte thickening with increasing sarcomeres and concentric LVH. LVH increases myocardial oxygen demand which can contribute to the symptoms of severe AS. Supply-demand mismatch on exertion may trigger exertional angina. Syncope may occur due to reduced cerebral perfusion on exertion when cardiac output in unable to increase adequately to meet increased peripheral demands due to the fixed obstruction[5,79].

As AS longitudinally progresses from mild to moderate to severe, compensatory mechanisms can no longer overcome outflow resistance and stroke volume reduces. This is exacerbated by progressive LVH as increased ventricular stiffness prevents normal ventricular filling, and declining myocyte function with fibrosis reduces LVEF[5,79].

This pathology leads to compensatory mechanisms and activation of the neurohormonal axis results. Studies confirm abnormal ANS function and excess RAAS activation in patients with severe aortic stenosis[33]. Although ACE inhibition has not been shown to slow the degree of AS progression, it can improve the degree of LVH[80].

Preclinical and clinical studies of AS confirm ANS derangement, both sympathetic and parasympathetic. Heart rate parameters that include HRT, deceleration capacity (DC), HRV and vagal response to deep breathing are deranged and correlate with degree of LVH, diastolic dysfunction, New York Heart Association class, impaired LVEF and abnormal biomarkers (troponin and BNP)[81–83].

Furthermore ANS derangement predicts increased mortality risk in patients with severe AS. Duckheim et al assessed deceleration capacity (DC) in 374 patients undergoing transcatheter aortic valve implantation (TAVI). In patients with impaired DC <2.5ms, 1 year mortality was significantly higher than those with a DC >2.5ms (23.3% vs 8.5%, $P < 0.001$). They postulated that DC assessment in patients with symptomatic severe AS may identify patients at higher mortality risk[84].

C.Z Zheurn et al. conducted a study in 300 patients with severe AS. They assessed HRT and DC and diagnosed severe autonomic failure (SAF) if both were abnormal. Two-year mortality was 50% among patients with severe AS and SAF. They concluded that autonomic function testing may identify patients at higher risk of mortality who warrant earlier intervention though asymptomatic[85].

Small studies of patients with AS have assessed other autonomic function

parameters. Elevated MSNA levels were noted at rest in 14 patients with severe AS due to undergo TAVI versus controls (61.0 ± 1.7 burst/min vs. 55.4 ± 1.4 burst/min; $p < 0.05$). These levels reduced to control levels when reassessed one week post TAVI[86].

L Compostella et al. reviewed HRV in 129 patients post-surgical aortic valve replacement (SAVR) and 82 patients post transfemoral or transapical TAVI, and showed that patients post SAVR had significantly impaired HRV versus those done less invasively. They proposed a minimally invasive approach may be favourable in patients with dysregulated autonomic function[87].

Studies on MIBG scanning in AS and valve replacement have yielded some conflicting though thought provoking results. A single centre in Japan showed baseline impairment in late H/M ratio and WR pre-TAVI in 67 patients with severe AS that improved at 2 weeks post-TAVI. A follow on similar study of 75 patients imaged at baseline, 2 weeks and 6 months post TAVI showed ongoing improvements in late H/M ratio at 6 months, and a stable improvement in WR. The authors suggested that TAVI has a positive impact of SNS dysfunction in patients with severe AS. When correlated with TTE imaging, they note that the higher mean peak aortic valve gradient, the more likely the patient was to have significant improvement in H/M ratio[88,89].

Another study of 22 patients with severe LVH and AS compared MIBG imaging to 14 patients with hypertension and 10 controls. They showed similar abnormalities on MIBG imaging among patients with AS and those with HTN and noted no improvement in MIBG imaging 6 months post TAVI in 10/22 patients imaged at that time point, perhaps suggesting there may be a cut off in adverse remodelling where the LV can no longer positively remodel post intervention[90].

A review of 44 post TAVI patients showed that patient-prosthesis mismatch (PPM) identified on TTE was a negative predictor for late H/M ratio and WR improvements on MIBG imaging when compared to patients without PPM. They hypothesised that an undersized aortic valve replacement and resultant outflow obstruction may cause ongoing excess sympathetic activation [91].

Conclusion

Autonomic dysregulation plays a significant role in many cardiovascular pathologies. Improved ANS testing methods have improved our understanding of the association. Among cardiovascular pathologies, management of severe AS remains challenging and particularly among asymptomatic patients. Autonomic dysfunction in this cohort correlates with mortality risk and may improve risk stratification. Larger studies are required to determine if early intervention in asymptomatic patients with severe AS and autonomic dysfunction will improve outcome.

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Funding Statement
None

Conflict of Interest
The authors have no conflicts of interest to declare

Acknowledgements
None

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