TACHYCARDIA - SIGNIFICANCE

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Tachycardia - Significance

ANCC Accredited NCPD Hours: 2.4 hrs

Target Audience: RN/APRN

Need Assessment

A life threatening arrhythmia is a medical condition that requires immediate intervention. In critical care settings, nurses play a critical role in arrhythmia identification and tachycardia management. Efforts are needed to increase and maintain the knowledge of arrhythmias, significance of tachycardia, ECG and rhythm interpretations and nurse's knowledge and skills should not diminish with time.

Objectives

- Describe the Physiology and ion channel mechanisms involved in tachycardia.
- Analyse the etiological factors of tachycardia.
- Discuss the major types of tachycardia.
- Describe the diagnosis and differential diagnoses of tachycardia.
- Analyse utilization of Activation mapping in detection of tachycardia.
- Explain the management of tachycardia
- Recognise the role of implantable cardioverter defibrillator (ICD) in tachycardia management and its detection criteria
- Explain Tachycardia-induced cardiomyopathy and its management

Goal

The goal of this article is to fulfil the education requirement on the laws and rules that govern the practice of nursing in Florida for all levels of nursing

Introduction

Paroxysmal tachycardia is a common condition in patients. Both cardiac and non-cardiac diseases, such as anoxia, hydropenia and electrolyte imbalance, can induce arrhythmias. Persistent tachycardia can result in serious and potentially fatal pathologies such as heart failure; therefore, timely and effective treatment is of great clinical significance. However, the subjective symptoms of tachycardia, such as a choking sensation in the chest or palpitations, are not as evident in pediatric patients, particularly infants, as those in adult patients. This can lead to missed treatment opportunities and can result in severe complications, including arrhythmia, cardiomyopathy and sudden mortality. Thus, finding novel, specific biomarkers of tachycardia has great implications for the early prevention and treatment of this condition and may reduce the chance of sudden mortality caused by malignant arrhythmias. At present, the treatment of arrhythmias primarily involves drug therapy and radiofrequency catheter ablation. However, this methodology is not preferred for pediatric patients since the organs of the patients are still undergoing development and vascular complications can occur and in recentyears, clinical studies have begun attempts to control paroxysmal or persistent tachycardia in by gene-targeted therapy, with the aim of improving cardiac function especially in affected children. [1, Rank 5]

Tachycardia

Tachycardia, conventionally, but arbitrarily, defined as an atrial and/or ventricular rate of >100 beats per minute. It can be physiological or pathological in origin. Various adverse consequences from tachycardia have been recognized, and an important one is the association between persistent tachycardia and cardiomyopathy.

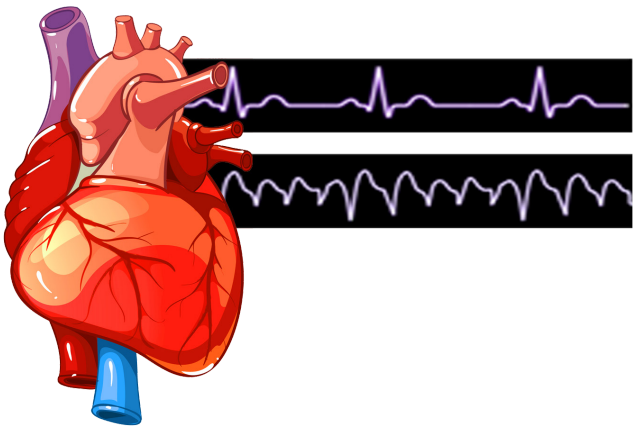

Figure 1: Ventricular tachycardia

Physiology: Ion Channels in Sinoatrial Node Function

Automaticity of Sinoatrial node (SAN) is dependent on two closely coupled clocks, voltage- and calcium-dependent mechanisms. The voltage- dependent

mechanism involves the funny current (If) mediated by HCN channels located at the plasma membrane. If has several unusual properties for a transmembrane current, including activation by a hyperpolarized voltage, permeability to both Na+ and K+ ions, regulation by intracellular cAMP, and small single channel conductance. There are four recognized HCN channel isoforms (1 to 4). HCN4 is the predominant subtype found in the SAN. By contrast, the Ca2+-mediated mechanism involves rhythmic release of Ca2+ from the sarcoplasmic reticulum (SR), subsequent reuptake by the SR Ca2+-ATPase and extrusion via the Na+-Ca2+ exchanger. Together, the complex interplay of ion channels and pumps gives rise to the pacemaker action potential (AP), which is uniquely characterized by spontaneous depolarization during phase 4. [2, Rank 3]

Na+ channels are found in high numbers in the periphery of the SAN, where they are thought to play a role in exit conduction of APs to the atrium. Each Na+ channel is formed by a pore-forming α-subunit, a modulatory β-subunit and additional regulatory proteins. The NaV1.5 α-subunit, encoded by SCN5A, has four domains (I to IV), each of which contain six transmembrane segments (S1 to S6). The positive-charged S4 segments undergo outward movement upon membrane depolarization, opening the central pore to allow Na+ entry. The resulting INa therefore partly determines myocardial excitability and conduction velocity of the APs. Late INa results in membrane depolarization in the atrial myocardium, which produces fast inactivation, by moving the linker region between domains III and IV to occlude the central pore. This is followed by slow inactivation, where the P-segment linker sequence between S5 and S6 bends back into the plasma membrane lining the outer region of the pore. The precision of sodium channel function is vital for the maintenance of transmembrane electrochemical gradient and therefore cardiac function. [3, Rank 4]

Other ion channels are also involved in SAN function, such as HCN channels, predominantly HCN4, carry the If current which is a combination of both sodium and potassium currents. Alterations in the highly regulated activation and inactivation of the highly regulated cycle of ion channels, such as an increase in late INa can lead to arrhythmias. A genetic mutation in any part of this complex pathway results in SAN dysfunction leading to arrhythmias. [4, Rank 3]

Conduction of APs from one myocyte to the next occurs via gap junctions, each of which consists of two hexamers of connexin (Cx) subunits. Cx 30.2, 40, 43 and 45 are found in cardiac tissues. Cx40 is expressed only in the atria and His-Purkinje system. Cx43 is expressed throughout the atria and ventricles. Cx45 is the predominant isoform found in the core of SAN, whereas Cx43, Cx40 and Cx45 are expressed in the periphery. However, few gap junctions are found in the SAN core, suggesting that intercellular coupling is not required for synchronization of electrical activity within the node.

The conventional membrane voltage-dependent gating, transjunctional voltage-dependent gating, phosphorylation, intracellular Ca2+ and pH (69 as well as the surrounding lipid environment all regulate gap junctional conductance. [5, Rank 5]

Arrhythmias and Tachycardia

Any persistent tachycardia (as shown in figure 2) can result in cardiomyopathy. Atrial fibrillation with persistent rapid ventricular rates is the most common cause. Sinus tachycardia and Postural tachycardia

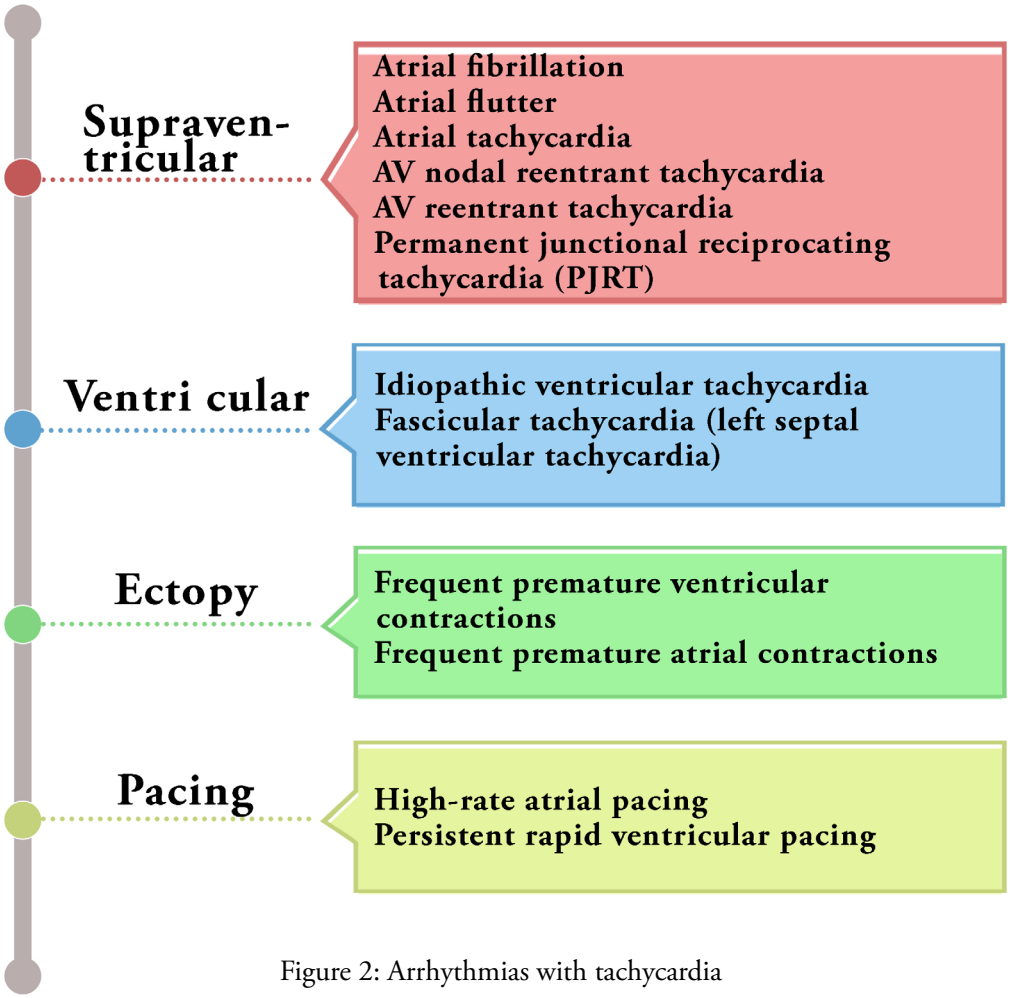

Figure 2: Arrhythmias with tachycardia

syndrome are usually not associated with cardiomyopathy for unclear reasons. Thyrotoxicosis resulting in persistent sinus tachycardia or atrial fibrillation and consequent high output heart failure does not usually cause tachycardial cardiomyopathy.

Aetiology of Tachycardia

Tachycardia can have physiological or pathological causes. Physiologically it is commonly associated with catecholaminergic triggers, including exercise, stress, pain, and anxiety. Pathologically, there are cardiac and non-cardiac etiologies as summarized below. (as shown in Figure 3 and 4)

Ventricular tachycardia is an arrhythmia that originates in the ventricles as demonstrated by a wide QRS on an electrocardiogram. It can be nonsustained (lasting less than 30 seconds or sustained (lasting greater than 30 seconds or with associated hemodynamic instability).

Risk factors for torsades de pointes include medications that prolong the QT interval, female gender, hypokalemia, hypocalcemia, hypomagnesemia, ischemia, and structural heart disease. Myocarditis is an inflammatory process involving cardiac myocytes that is generally secondary to a viral infection. Other sources of myocarditis include bacterial and parasitic infection,

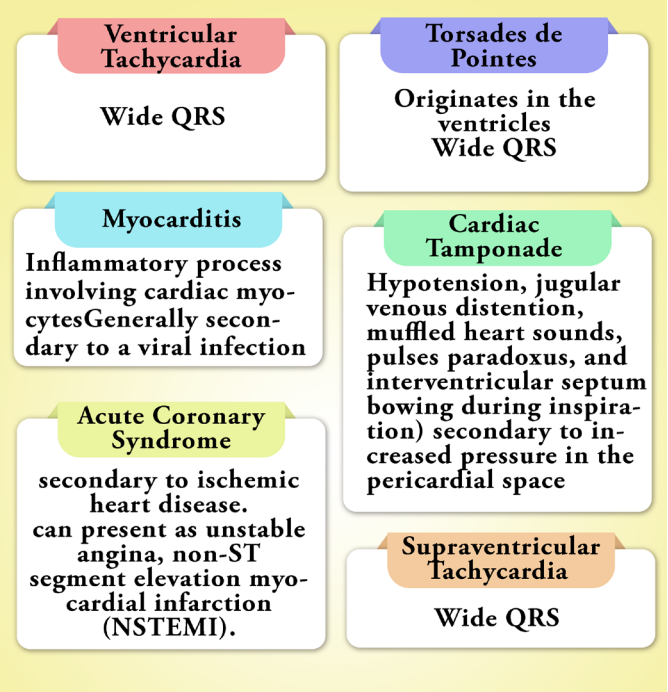

Figure 3: Cardiac etiologies of tachycardia

ingestion of medication or recreational substance, hypersensitivity reactions to medications or venoms, autoimmune disease, sarcoidosis, hypothermia, ischemia, radiation, and rejection of a transplanted heart. Patients at elevated risk for acute coronary syndrome are patients with obesity, hypercholesterolemia, hypertension, diabetes mellitus, age greater than 50 years, male gender, tobacco use, and a family history of heart disease.

Major non-cardiac pathology is respiratory. Pulmonary Emboli are disorders can be acute, chronic, or both and acute pulmonary emboli are generally more clinically significant and have higher rates of morbidity and mortality. Hypoxia is a clinical state where tissues do not receive

Non Cardiac Aetiology of Tachycardia

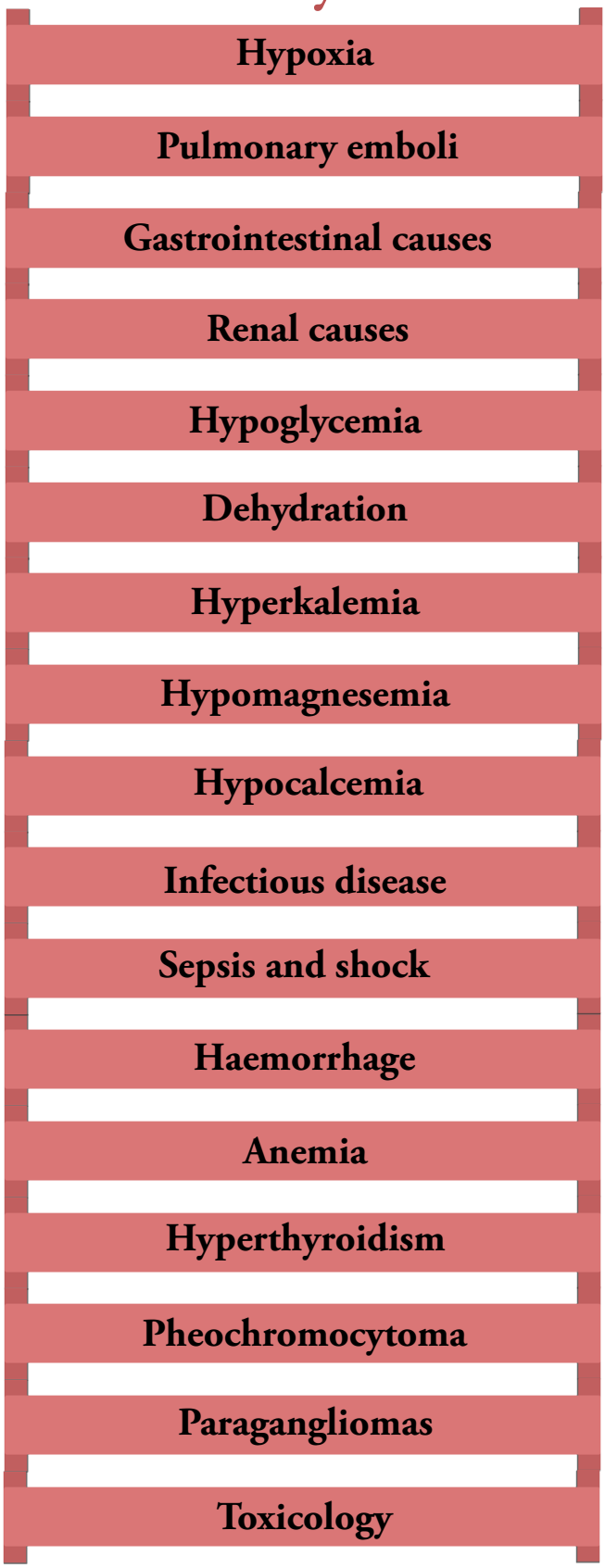

Figure 4: Non – cardiac causes of Tachycardia

the necessary amount of oxygen to support their metabolic demand. Hypoxia can result from the inability to take in oxygen, transport the oxygen, or perform oxygen gas exchange. Hypoglycemia is the state when plasma glucose concentration falls below 70 mg/dL. Dehydration results from an imbalance of the total body fluid intake and output. To maintain cardiac output in the setting of intravascular depletion, heart rate will increase.

Hypomagnesemia is a serum magnesium level below 1.6 mg/dL. Hypomagnesemia can result from the low intake or poor absorption of magnesium, and increased filtration or excretion of magnesium. Hypocalcemia is a serum calcium level below 8.5 mg/dL. It can result from lack of sunlight exposure, nutritional deficiency, malabsorption, post-gastric bypass surgery, end-stage liver disease, chronic kidney disease, vitamin-D dependent rickets, hypomagnesemia, hyperphosphatemia, medications, and rapid transfusion of large volumes of citrate-containing blood, acute critical illness, osteo-blastic metastases, acute pancreatitis, rhabdo-myolysis, and mitochondrial gene defects.

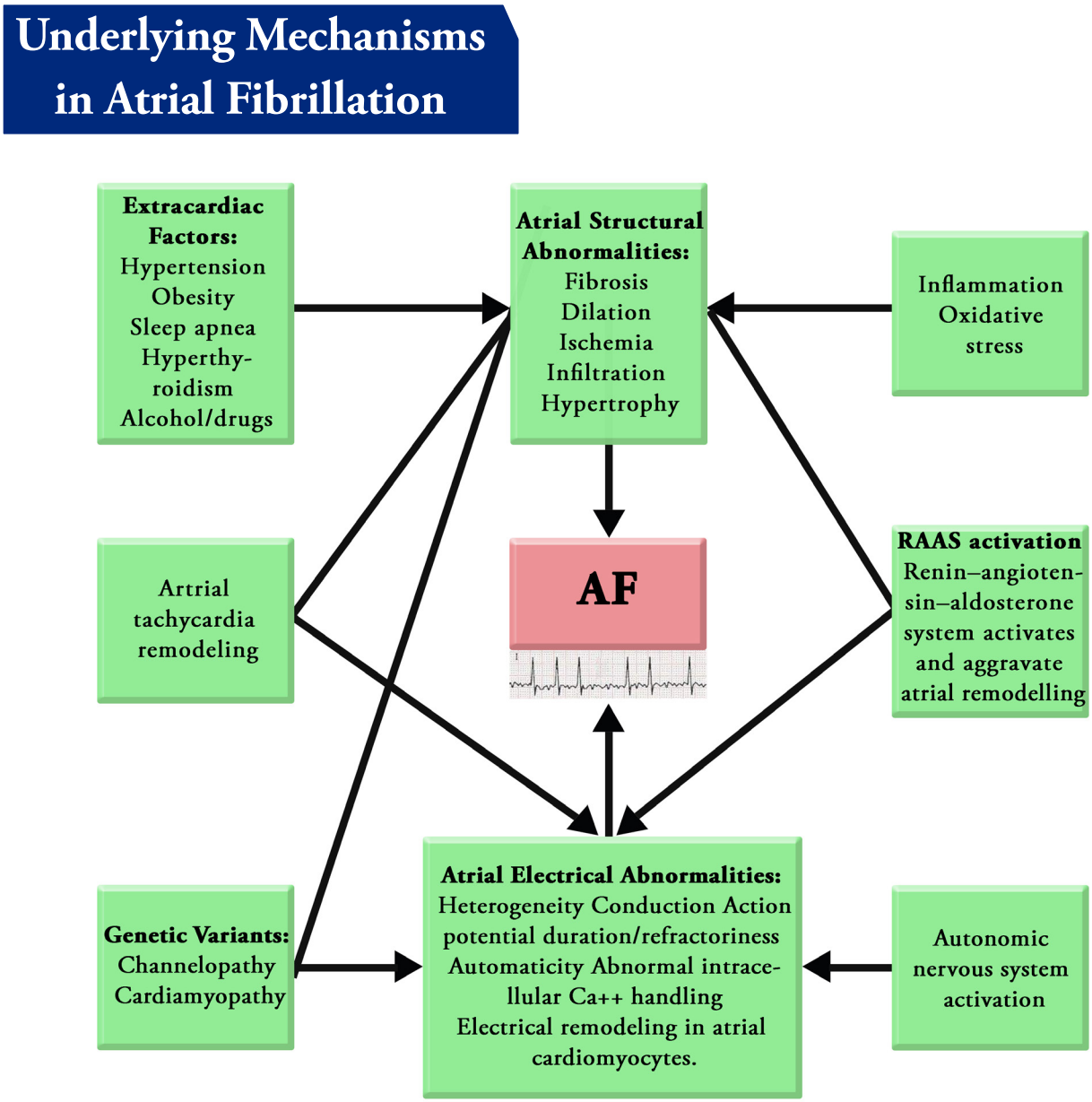

Figure 5: Mechanism in AF

Atrial Fibrillation occurrence is dependent upon complex electrical defects in the atria which include a rapidly firing focus, complex multiple reentrant circuit, or rotors. Alterations in after-depolarization, both early and late, can contribute to ectopic atrial foci. Reentrant waves can occur due to reduced refractoriness, slow conduction, and conduction barriers. Rotors, or localized electrical spiral waves, are a result of complex substrate changes leading to a stable disease wave. These electrical defects are dependent upon remodeling mechanisms, which can be grouped into electrical, structural, and autonomic remodeling that allow for initiation and maintenance of Atrial Fibrillation. [15, Rank 3]

> "In supraventricular tachycardia, if the rhythm is regular, atrial flutter, atrioventricular re-entrant tachy cardia (AVRT), atrioventricular nodal reentrant tachycardia (AVNRT), atrial tachycardia, or sinus tachycardia are the common etiologies. If the rhythm is irregular atrial fibrillation, atrial tachycardia with variable block, atrial flutter with variable block, multifocal atrial tachycardia, or frequent premature atrial contractions should be the cause."

Electrical Remodelling

One of the most characterized mechanisms driving Atrial Fibrillation is the electrical remodeling occurring in atrial cardiomyocytes. Various types of ionic currents have been found to change in AF and, through animal models, to contribute to its development. The ionic currents include the L-type Ca2+ current and inward rectifier K+ currents. Gap junction function, specifically connexins 40 and 43, has also been linked to lone AF, though this may have broader effects on conduction.

Alterations in Ca2+ handling in the atria can contribute to both development and worsening of AF. Numerous studies have shown the connection between altered calcium handling and delayed afterdepolarizations, which contribute to formation of ectopic foci and AF initiation. In cardiomyocytes, intracellular calcium is stored in the sarcoplasmic reticulum (SR) until its release is triggered by specific stimuli. In Atrial Fibrillation, unwarranted calcium release can be triggered by ryanodine receptor (RyR) hypersensitivity or sarcoplasmic reticulum Ca2+ overload. Both ryanodine receptor hyperphosphorylation and mutations have been shown to increase Ca2+-sensitivity. Data from mouse models also support the role of excessive ryanodine receptor activation in development of AF. This is also reflected in patients harboring activating mutations in ryanodine receptor that exhibit catecholaminergic polymorphic ventricular tachycardia and Atrial Fibrillation. Mice specifically lacking the ryanodine receptor stabilizing subunit FK-BP12.6 exhibit sarcoplasmic reticulum Ca2+ leaks and increased susceptibility to Atrial Fibrillation. AF itself can also promote calcium handling defects, as has been observed in chronic Atrial Fibrillation patients who display activation of the Ca2+ calmodulin-dependent protein kinase type II (CaMKII) leading to phosphorylation

of ryanodine receptors. Studies in isolated canine atrial cardiomyocytes have revealed detrimental effects of tachypacing on calcium handling. As atrial depolarization rates increase, intracellular Ca2+begins to accumulate, leading to activation of calcineurin/NFAT signaling, which in turn leads to reduced transcription of Cav1.2 L-type calcium channel (CACNA1C), ultimately leading to reduced L-type Ca2+current. Animal models have shown this leads to a reduced action potential duration and atrial effective refractory period, which favors reentrant waves. [17, Rank 4

Increased K+ currents are intimately associated with electrical remodeling in Atrial Fibrillation. The inward rectifier K+ currents (IK1, and IK,AcH, basal, and acetylcholine dependent, respectively) are increased in AF which alters resting potential and phase 3 activation, leading to reduced atrial refractoriness and wavelength. This mechanism has also been supported by in vitro data showing increased magnitude of inward rectifier K+ currents stabilizing reentrant currents. The elevated K+ currents observed in Atrial Fibrillation are likely due to upregulation of the Kir2.1 channel, a major channel protein for IK1current, which has specifically been shown to be affected in Atrial Fibrillation. It has been hypothesized that regulation of Kir2.1 is controlled by miRNA targeting Kir2.1, specifically miR-1 and miR-26, which are reduced in Atrial Fibrillation. Thus in Atrial Fibrillation, loss of miR-1 and miR-26 would lead to increased K+ channels and current, leading to reduced atrial refractoriness and wavelength and ultimately allowing for reentrant waves.

Gap junction function is also affected in AF. Gap junction function is directly related to conduction velocity, which is a known determinant of Atrial Fibrillation. Specifically, slower conduction velocity favors reentry, allowing for initiation and maintenance of Atrial Fibrillation. From clinical studies, GJA5, which codes for connexin 40, has been linked to idiopathic Atrial Fibrillation. Heterogeneous connexin 40 distribution has also been observed in large animal models of Atrial Fibrillation, specifically in goats undergoing endocardial burst pacing, suggesting that connexin 40 remodeling is involved in maintenance of AF. In dogs undergoing atrial tachypacing, connexin 40 has been shown to decrease in the pulmonary vein, a region shown to be an important site for reentrant waves. Furthermore, mutations in the GJA5 promoter sequence have been associated with Atrial Fibrillation vulnerability through human clinical studies. Somatic mutations in GJA1, which codes for connexin 43, have been observed specifically in the atria, a phenomenon referred to as genetic

mosaicism. The mutant connexin 43 contributes to heterogeneous electrical conduction, which favors reentrant waves and ultimately leads to Atrial Fibrillation. The gap junction inhibitory peptide, rotigaptide, has been used in dog models of Atrial Fibrillation to varying degrees of success. Rotigaptide was shown to have beneficial effects on Atrial Fibrillation in the setting of acute ischemia but not when caused by ventricular or atrial tachypacing, suggesting that gap junction inhibition may only be necessary for specific stages or etiologies of Atrial Fibrillation, as reflected in its varying roles in different experimental models of AF. [14, Rank 4]

Electrical changes in the heart, as would be expected based on the principles of excitation-contraction coupling, lead to secondary changes in contractile function in the atria. This is broadly demonstrated by the association of chronic Atrial Fibrillation with atrial contractile dysfunction, which has been observed as a reduction in maximum tension as well as in the rates of tension activation and relaxation. These effects have been linked to increased myofilament sensitivity to Ca2+, possibly due to changes in myofilament phosphorylation. These effects are also accompanied by a reduction in myofibril passive tension, potentially caused by upregulation of slow beta-myosin heavy chain isoform and the more compliant titin isoform N2BA. However, these myofibril alterations may be related to specific mechanisms of Atrial Fibrillation development, as a dog model of Atrial Fibrillation induced via atrial tachycardia developed hypocontractile atria while other models of AF have reported no changes in myofibril properties. Recent studies have also identified a role for inositol-1,4,5-trisphosphate-receptor (IP3R)-mediated Ca2+ release in Atrial Fibrillation -related contractile defects which may represent a mechanism independent of myofibril alterations. [16, Rank 2]

Structural Remodelling

Structural remodeling is perhaps the most obvious change in the atria that occurs in Atrial Fibrillation. These effects are characterized by changes is tissue properties (most notably fibrosis), atrial size, and cellular ultrastructure. These types of changes predispose the atria to defects in conduction predominantly contributing to reentry and rotor formation.

Various factors contribute to the fibrosis underlying Atrial Fibrillation, including cell stretch, neurohumoral activity, oxidative stress, and even Atrial Fibrillation itself can contribute to worsening tissue properties. Atrial fibrosis is a salient

feature of a majority of animal models of Atrial Fibrillation, including aging, myocardial infarction (MI), volume overload, endurance exercise training, and tachypacing-induced HF. Conversely, numerous animal models of atrial fibrosis exhibit increased susceptibility to Atrial Fibrillation. Specific profibrotic signaling molecules are associated with atrial fibrosis and Atrial Fibrillation including Angiotensin II, aldosterone, and TGF-β1.

Angiotensin II functions in the renin-angiotensin-aldosterone system (RAAS) and increases in activity have previously been associated with increased cardiac fibrosis. Studies showed increased levels of angiotensin-converting enzyme (ACE) in AF and corresponding increased levels of activated extracellular signal-regulated kinase 1 and 2 (ERK1/2), consistent with increased RAAS activity. Conversely, treatment with candesartan, an angiotensin receptor blocker, reduces the profibrotic effects of rapid atrial pacing induced Atrial Fibrillation and reduces propensity for Atrial Fibrillation. Similar results were also observed with the ACE inhibitor enalapril. In dogs with ventricular tachypacing-induced congestive heart failure (CHF), atria exhibit conduction slowing, fibrosis, and propensity for atrial burst-pacing induced Atrial Fibrillation, which occur along with increased atrial concentration of angiotensin II. With enalapril treatment, all of these features are attenuated, supporting the importance of RAAS signaling in developing AF features. [13, Rank 3]

Aldosterone, another important mediator of RAAS (Renin–angiotensin–aldosterone system) signaling that binds to the mineralocorticoid receptor (MR), has also been linked to atrial fibrosis and AF. Blockade of aldosterone signaling at the MR via spironolactone improved morbidity and mortality in Atrial Fibrillation patients, suggesting an important role for aldosterone in Atrial Fibrillation. Another MR blocking drug, eplerenone, has also been successfully used to prevent recurrence of Atrial Fibrillation after catheter ablation. The effects of MR blockade on atrial fibrosis have not been directly examined in patients; however, data from animal and cell-based models of Atrial Fibrillation have demonstrated reductions in cardiac fibrosis following treatment with MR (mineralocorticoid-receptor) blockers.

TGF-β1 is another profibrotic molecule upregulated in Atrial Fibrillation, as demonstrated in animal models of Atrial Fibrillation as well as in clinical studies on patients with AF. TGF-β1 is an established positive regulator of cardiac fibrosis and its specific overexpression in the heart leads to atrial fibrosis and increased susceptibility to Atrial Fibrillation, suggesting that TGF-β1

is sufficient for developing an Atrial Fibrillation -prone substrate. However, the determinants of increased TGF-β1 expression in the heart during AF are still unknown.

Evidence from genetic models of cardiac fibrosis suggest that the atria are particularly sensitive to profibrotic signaling potentially due to increased response of atrial fibroblasts compared to ventricular fibroblasts. This may be related to the cases of atrial fibrosis without ventricular fibrosis in patients with lone Atrial Fibrillation. This has been further explored in transgenic mouse studies overexpressing either ACE or a constitutively active TGF-β1 mutant protein in the heart. Both of these models lead to fibrosis only in the atria.

MicroRNAs have also been linked to control of atrial fibrosis leading to Atrial Fibrillation. miR-21 knockdown suppressed the development of an AF substrate in a rat model of post-MI heart failure. This is hypothesized to occur via miR-21's role in regulating Sprouty-1 levels, which negatively regulate ERK 1/2 activity, which then inhibits fibroblast density. [12, Rank 4]

The mechanism by which fibrotic tissue serves as a substrate for Atrial Fibrillation has been examined in detail. Cardiomyocytes in fibrotic atria are more distantly separated than those in nondiseased atria, with the fibroblasts and cardiac extracellular matrix essentially forming a physical conduction barrier. This reduces electrical coupling between cardiomyocytes and provides susceptibility to reentry. There is also an increase in fibroblast proliferation in AF and as with other disease states; their proliferation in AF is linked to increases in myofibroblast phenotype. Interactions specifically between myofibroblasts and cardiomyocytes have previously been shown in cocultures to negatively affect conduction organization leading to increased propensity to ectopic activity and reentrant arrhythmias.

From early on in the history of Atrial Fibrillation research, increased atrial size has been known to favor Atrial Fibrillation. Reentrant circuits form more readily with larger atrial size, potentially due to the additional area available for rotor formation as demonstrated in computer modeling studies. Animal models, as well as clinical data support this idea. Atrial size may also indirectly affect tissue properties, since it can be a sign of increased atrial stretch, which is generally associated with increased tissue remodeling in the atria.

Structural remodeling changes in AF also occur at the ultrastructural level. Numerous defects in cardiomyocyte ultrastructure have been observed in AF including myolysis, glycogen accumulation, as well as changes in nuclear chromatin, mitochondrial disruption and redistribution as

well as SR alterations. Gap junction localization heterogeneity, specifically of connexin 40, is also observed in Atrial Fibrillation models. Interestingly, many of these changes can partially revert back to normal after restoration of sinus rhythm. In a goat model of burst pacing-induced Atrial Fibrillation, typical ultrastructural defects appear after 4 months of Atrial Fibrillation, but after restoration of normal sinus rhythm for 2 months myolysis, glycogen accumulation, and mitochondrial defects are improved and nuclear chromatin defects are completely normalized. [10, Rank 5]

Autonomic Remodelling

The autonomic nervous system exerts significant control of cardiac electrophysiology, and defects in autonomic function have been associated with Atrial Fibrillation. The heart is extensively innervated by the autonomic nervous system by both extrinsic (ganglia outside the heart) and intrinsic (ganglia inside the heart) nervous tissue. The extrinsic nerves include the vagal nerve and nerves arising from the paravertebral ganglion, which includes the thoracic ganglion, cervicothoracic ganglion, middle cervical ganglion, and the superior cervical ganglion.

There is extensive evidence of autonomic dysfunction reflected as increased sympathetic activity in Atrial Fibrillation observed in various types of large animal Atrial Fibrillation models. In a dog model of pacing-induced Atrial Fibrillation, ***heterogeneous increased sympathetic enervation has been observed in the atria.*** In ventricular MI-associated Atrial Fibrillation, atrial nerve sprouting and sympathetic hyperinnervation have been observed. In a pacing-induced CHF model of ***paroxysmal Atrial Fibrillation, increased autonomic nerve activity was observed.*** Sympathetic innervation of the atria appears to be particularly sensitive to pacing, as observed in an intermittent left atrial tachypacing model which causes sympathetic hyperinnervation, paroxysmal Atrial Fibrillation, and paroxysmal atrial tachycardia. The role of sympathetic innervation is further supported by the observation that simultaneous sympathovagal discharge commonly precedes Atrial Fibrillation. Autonomic changes have also been observed in smaller model systems such as in rats where endurance exercise increased Atrial Fibrillation susceptibility in the context of autonomic changes, atrial dilation, and fibrosis. This effect is also paralleled in humans by the increased prevalence of Atrial Fibrillation in endurance athletes. Though there is much evidence of

autonomic remodeling occurring, there is less data directly testing the role of autonomic remodeling on development and progression of Atrial Fibrillation, though there is suggestion that the increased sympathetic activity leads to heterogeneous changes in atrial refractoriness which in turn favor reentrant waves. [12, Rank 4]

Ablation of various autonomic innervation sites has revealed the necessity for their function in the maintenance of Atrial Fibrillation. Vagal nerve stimulation has been effective in suppressing induction of Atrial Fibrillation in an induced model of Atrial Fibrillation. Innervation by nerves beside the vagal nerve has also been explored to similar results. Ablation of the ganglionated plexus can also improve long-term Atrial Fibrillation symptoms. This has also been shown with specific denervation of the pulmonary vein. Renal sympathetic denervation has also been shown to improve Atrial Fibrillation features; however this may also affect nonautonomic mechanisms such as RAAS signaling. Somatic

sensory modulation via low level stimulation to the tragus nerve of the ear has also been shown to improve early stages of Atrial Fibrillation; however, the mechanism by which this occurs is currently unknown. Based on these studies, autonomic innervation appears to function as an exacerbating factor in Atrial Fibrillation as ablation improves Atrial Fibrillation severity and delays onset; however, it is unable to prevent or reverse Atrial Fibrillation, suggesting that the targeted forms of autonomic remodeling are not required for Atrial Fibrillation. [11, Rank 3]

Altered Ionic Currents

HCN4 is involved in mammalian cardiac pacemaking and is predominantly expressed in the SAN. Loss-of-function HCN4 mutations are known to cause atrioventricular (AV) block, long QT syndrome (LQTS), AF, familial TBS (Tachycardia-bradycardia syndrome) and non-compaction cardiomyopathy in addition to sinus bradycardia. The G1097W HCN4 mutation, which is a loss-of-function mutation resulting in a hyperpolarizing shift of the activation curve and reduced expression levels, demonstrates 4:1 AV block and reflex sinus tachycardia. A missense HCN4 mutation was found to lead to impaired trafficking of the channel to the surface membrane, resulting in SSS, long QT and torsade de pointes. Some of these phenotypes have been recapitulated in genetically modified mice, making them particularly useful for modeling Tachycardia-bradycardia syndrome.

Mutations in the SCN5A encoding for the Na+ channels can lead to a range of clinical phenotypes, including SSS, Brugada syndrome, LQTS type 3, AVN block, dilated cardio-myopathy, AF and overlap syndromes. In a newborn patient, a gain-of-function SCN5A mutation producing a persistent inward Na+ current was found to cause LQTS type 3, and alternating tachycardia-bradycardia of 2:1 AV block and ventricular tachycardia have been observed. Individuals with loss-of-function SCN5A mutations can suffer from SSS and Brugada syndrome, which are responsible for bradycardic and tachycardic complications, respectively. [29, Rank 2]

Upregulation of the inward rectifier current (IK1) results from reduced levels of microRNA-1, observed in heart failure. This causes membrane hyperpolarization, bradycardia and shortening of APs that predisposes to atrial reentry. Ankyrin-B, a member of the ankyrin family, is expressed at high levels in the SAN and has functions such as cell signaling and assembly of ion channels in the plasma membrane. Humans with ANK2 gene variants suffer from SND, AF and prolonged QT intervals. Ankyrin-B normally forms a complex with Na+-K+ ATPase, the Na+-Ca2+exchanger and the IP3 receptor. Loss of ankyrin-B therefore leads to impaired Ca2+ transport across the SR and plasma membranes.

Finally, a loss-of-function mutation in the Ca2+ channel gene has also been shown to cause Tachycardia-bradycardia syndrome. Normally, Ca2+ entry through L-type Ca2+ channels plays a role in pacemaker activity by contributing to diastolic depolarization. Reduction in this current can reduce the degree of spontaneous depolarization, slow pacemaker activity and increase the likelihood of spontaneous arrhythmias in SAN cells. [30, Rank 5]

Supraventricular tachycardia

Supraventricular tachycardia (SVT) includes a variety of types of re-entrant fast heart rhythms originating in any part of the heart's conduction system above the ventricles. The major types of SVT include: atrioventricular nodal reentrant tachycardia, atrioventricular reciprocating tachycardia, atrial tachycardia, inappropriate sinus tachycardia, and atrial flutter.

Supraventricular tachycardia (SVT), also called paroxysmal supraventricular tachycardia, is defined as an abnormally fast heartbeat. It's a broad term that includes many forms of arrhythmias that originate above the ventricles (supraventricular) in the atria or AV node.

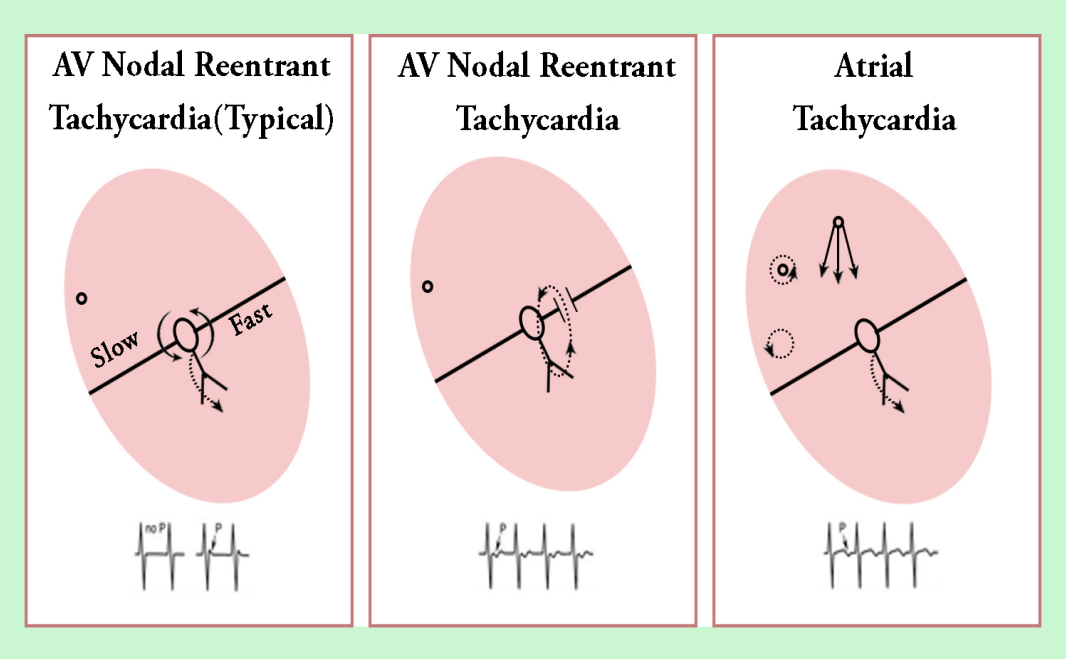

Figure 6: Mechanism in SVT

Physiologically atrial fibrillation is also a type of supraventricular tachycardia, but typically discussed outside of other SVT rhythms because of the complex differences between it and other supraventricular tachycardia rhythms. Atrioventricular nodal tachycardia is the most common type of supraventricular tachycardia, representing 50% to 90% of all supraventricular tachycardia cases. This type of supraventricular tachycardia, along with inappropriate sinus tachycardia, has a higher prevalence in women. Atrioventricular reciprocating tachycardia is the second most prevalent type of supraventricular tachycardia, accounting for approximately 33% of all supraventricular tachycardia. Atrioventricular reciprocating tachycardia and atrial flutter are seen more frequently in men.

Although the types of supraventricular tachycardia may differ in physiological mechanisms, the outcome of each is a rapid heartbeat that has a paroxysmal onset and termination. Supraventricular tachycardia episodes initially occur in late teens to early thirties, with a natural history of increasing episodic frequency over time. Duration of supraventricular tachycardia episodes vary widely from seconds to hours. Episodes are typically associated with symptoms of palpitations, dizziness, presyncope, nausea, anxiety, atypical chest pain, diaphoresis, and frank syncope. While clearly not as life-threatening as sudden cardiac death or other ventricular arrhythmias, many features of supraventricular tachycardia

make it particularly difficult and frustrating for patients to deal with. The unpredictability of the episodes and inability to control the disabling symptoms can render the patient incapacitated. Researchers have noted that up to 27% of supraventricular tachycardia patients stopped driving because of symptoms of near syncope or syncope. Patients with supraventricular tachycardia have averaged four hospital admissions or emergency department visits per year in the 2 years prior to radiofrequency ablation treatment. Investigators have also reported non-lethal cardiac arrest in 2% of supraventricular tachycardia subjects, with 16% requiring an electrical cardioversion to restore normal rhythm. [18, Rank 5]

Chronic antiarrhythmic drug therapy is the first line treatment for supraventricular tachycardia. However, these medications have a low long-term efficacy requiring frequent changes of drugs and/or dosages that can add to patients' frustration. Access to ablation procedures, performed by cardiac electrophysiology specialists, is acquired through a referral from a cardiologist or primary care provider.

Despite the highly specified symptomatic and EKG diagnostic criteria, diagnosis and referral for ablation treatment is not always straightforward. Researchers have noted that the symptoms commonly reported by patients with supraventricular tachycardia mimic other conditions and are often mistaken for anxiety attacks or panic disorders, especially in women. Other researchers have noted gender related differences in referral patterns for radiofrequency ablation procedures. Due to the sporadic nature of the episodes, it may be difficult and time consuming to capture the supraventricular tachycardia on an EKG or ambulatory cardiac monitoring. If patients are misdiagnosed, they are not referred in a timely manner for curative ablation therapy. If the supraventricular tachycardia is not diagnosed correctly, patients' lives may be affected tremendously by these not only intrusive, but potentially life-threatening symptoms. Symptoms of supraventricular tachycardia may seem well understood clinically, but how the symptoms and supraventricular tachycardia episodes affect patients' lives has not been explored. [17, Rank 3]

Relationship Factors

HCN4 is involved in mammalian cardiac pacemaking and is predominantly expressed in the SAN. Loss-of-function HCN4 mutations are known to cause

atrioventricular (AV) block, long QT syndrome (LQTS), AF, familial Tachycardia-bradycardia syndrome and non-compaction cardiomyopathy in addition to sinus bradycardia. The G1097W HCN4 mutation, which is a loss-of-function mutation resulting in a hyperpolarizing shift of the activation curve and reduced expression levels, demonstrates 4:1 AV block and reflex sinus tachycardia. A missense HCN4 mutation was found to lead to impaired trafficking of the channel to the surface membrane, resulting in SSS, long QT and torsade de pointes. Some of these phenotypes have been recapitulated in genetically modified mice, making them particularly useful for modeling Tachycardia-bradycardia syndrome.

Mutations in the SCN5A encoding for the Na+ channels can lead to a range of clinical phenotypes, including SSS, Brugada syndrome, LQTS type 3, AVN block, dilated cardio-myopathy, atrial fibrillation and overlap syndromes. In a newborn patient, a gain-of-function SCN5A mutation producing a persistent inward Na+ current was found to cause LQTS type 3, and alternating tachycardia-bradycardia of 2:1 AV block and ventricular tachycardia have been observed. Individuals with loss-of-function SCN5A mutations can suffer from SSS and Brugada syndrome, which are responsible for bradycardic and tachycardic complications, respectively. [29, Rank 2]

Upregulation of the inward rectifier current (IK1) results from reduced levels of microRNA-1, observed in heart failure. This causes membrane hyperpolarization, bradycardia and shortening of APs that predisposes to atrial reentry. Ankyrin-B, a member of the ankyrin family, is expressed at high levels in the SAN and has functions such as cell signaling and assembly of ion channels in the plasma membrane. Humans with ANK2 gene variants suffer from SND, atrial fibrillation and prolonged QT intervals. Ankyrin-B normally forms a complex with Na+-K+ ATPase, the Na+-Ca2+exchanger and the IP3 receptor. Loss of ankyrin-B therefore leads to impaired Ca2+ transport across the SR and plasma membranes.

Finally, a loss-of-function mutation in the Ca2+ channel gene has also been shown to cause Tachycardia-bradycardia syndrome. Normally, Ca2+ entry through L-type Ca2+ channels plays a role in pacemaker activity by contributing to diastolic depolarization. Reduction in this current can reduce the degree of spontaneous depolarization, slow pacemaker activity and increase the likelihood of spontaneous arrhythmias in SAN cells. [30, Rank 5]

Diagnosis and Differential Diagnosis

Supraventricular Tachycardia

Traditionally SVT (defined as an atrial and/or ventricular rate >100 beats per minute [bpm] at rest involving tissue from the His bundle or above) includes AV reentry tachycardia (AVRT) due to accessory connections, AV nodal reentry tachycardia (AVNRT) and various forms of ATs including focal atrial tachycardias and MRATs. Most SVTs are regular and may manifest as narrow-QRS tachycardias (QRS duration <120 ms) or wide-QRS tachycardias (QRS duration >100 ms). Regular and paroxysmal palpitations with a sudden onset and termination are most likely related to AVRT or AVNRT. Termination by vagal manoeuvres further suggests a re-entrant tachycardia involving AV nodal tissue. Preexcitation on the surface ECG in a patient with regular paroxysmal palpitations strongly suggests AVRT, whereas irregular palpitations suggest AF or non-sustained atrial tachycardia. [22, Rank 4]

Narrow QRS Tachycardia

An ECG recorded during tachycardia is of key importance for an adequate diagnosis of SVT. Focal atrial tachycardia is an organised atrial rhythm usually ranging between 100 and 250 (rarely, up to a maximum of 300) bpm and the diagnosis is clear when the ventricular rate is lower than the atrial rate. An automatic atrial tachycardia is characterised by gradual acceleration of the atrial rate at tachycardia onset (warm-up phenomenon) and deceleration (cool down) before termination. Irregular R-R intervals during a tachycardia are consistent with atrial fibrillation if discernible P waves are absent, whereas although atrial flutter with varying degrees of conduction may also be irregular, it is often marked by a recurring pattern of 'grouped beating'. During Atrial tachycardia the conduction to the ventricles can be fast (1:1) or slow (3:1 or 4:1), but a 2:1 conducting atrial flutter should be strongly suspected for patients with ACHD with palpitations and seemingly inappropriately high heart rate, especially when there is a strong history of sinus node dysfunction. Although a discrete P wave with an intervening isoelectric interval suggests a focal Atrial tachycardia, an MRAT cannot be excluded in a patient with significant ACHD. [21, Rank 3]

Wide QRS Tachycardia

Wide-QRS tachycardias are most commonly (80 %) ventricular tachycardias (VTs), but can be SVT with bundle-branch block (BBB) aberration (15 %) or conduction over an accessory pathway (5 %). Diverse BBB morphology during wide-QRS tachycardia compared with sinus rhythm strongly favours ventricular tachycardias. Functional BBB is more frequently right sided because of its longer refractoriness. An accessory pathway may participate in the reentry circuit (antidromic AVRT) or act as a bystander during SVT (AT, atrial flutter, atrial fibrillation and AVNRT). Differential diagnosis should always be considered in the context of the underlying disease, with conditions such as Tetralogy of Fallot favouring ventricular tachycardias.

A 12-lead ECG during wide-QRS tachycardia showing ventriculo-atrial (VA) dissociation (atrial activity slower and independent of ventricular activity), is a major ECG criterion for VT. A 1:1 ventriculo-atrial conduction is found in up to 50 % of patients with ventricular tachycardia and gives no diagnostic clue. The QRS morphology during wide-QRS tachycardia may be useful for diagnosis in the absence of ventriculo-atrial dissociation, although conventional criteria may not apply as ventricular tachycardia morphology has not been systematically evaluated in this population. The differentiation between ventricular tachycardia and antidromic AVRT is difficult unless the surface ECG during sinus rhythm shows the same preexcitation pattern. SVTs conducted with aberrancy or antidromic AV re-entry tachycardia respond to vagal manoeuvres and adenosine, as described for narrow-QRS tachycardia. [22, Rank 3]

Ventricular Tachyarrhythmia Detection

Classification of cardiac signals is accomplished primarily by measuring cardiac cycle lengths (R-R, P R, and P P). In addition, the ICD (Implantable Cardioverter-Defibrillator) can also utilize abrupt changes in rate, irregularity of the cycle lengths and other criteria to further differentiate ventricular tachyarrhythmias. Each detected ventricular tachyarrhythmia is classified into one of the following zones:

VT-1 lower rate ventricular tachycardia,
VT-2 higher rate ventricular tachycardia, or
VF ventricular fibrillation.

Each zone is programmable to a separate rate with the zone limit defining the lowest rate in each zone. The upper rate limit of each zone is equal to the zone limit of the next higher class, creating a continuous range of rate classes. [16, Rank 4]

Ventricular Only Detection for VT

When a ventricular tachycardia zone is programmed, the ventricular-only detection algorithm uses a programmable ventricular tachycardia interval count and based on a rate/ interval cut-off criteria. This means that any time the rhythm crosses the programmed ventricular tachycardia detection interval, the ICD will classify the event as ventricular tachycardia. ventricular tachycardiadetection relies on simple up/down counters (i. e., separate for VT1 and VT2 zone), ventricular rate, and single-chamber enhancement. Detection enhancements such as Onset, Stability and Morph Match can be added to help to discriminate ventricular tachycardia from SVT. These detection enhancements are sometimes referred to as "therapy inhibitors", as both interval count and the programmed detection enhancement criteria must be met to classify an arrhythmia. The ventricular tachycardia detection counter determines the minimal number of ventricular tachycardia events for each zone

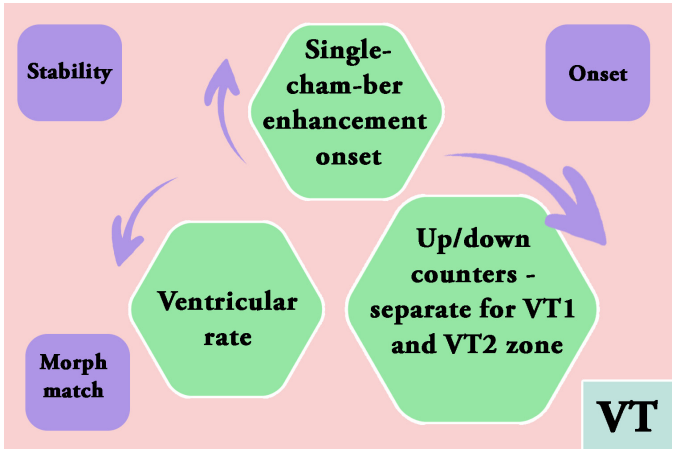

Figure 7: VT detection

that must be counted to initiate ventricular tachycardia detection and therapy delivery. The redetection counter of the VT1 zone must be greater than the redetection counter of VT2 zone and the "X" value of the VF zone detection counter. [18, Rank 3]

When Rate nly is used, detection is met when the programmed number of intervals exceeds the programmed detection count. Each time an interval is shorter than the programmed ventricular tachycardiazone limit, the ventricular tachycardia counter increments (+1). Conversely, the ventricular tachycardia counters decrement by one (–1) when an interval is longer than the programmed limit for that zone. All intervals in the VT2 zone will also increment the VT1 counter. Intervals longer than the defined detection zones decrement the counter for that zone. [19, Rank 4]

Stability is a detection enhancement to assist in determining if a tachyarrhythmia is ventricular tachycardia or atrial

fibrillation with a rapid ventricular response. Stability refers to the stability of R R intervals. Mono-morphic ventricular tachycardia demonstrates a stable R R interval, while in atrial fibrillation the R R intervals are typically unstable. Stability is evaluated on a beat-to-beat basis. Stability is used for detection and redetection. The Stability criterion is satisfied for a given ventricular interval when the difference between the current interval and each of the three preceding intervals is less than the programmed Stability limit. Unstable events reset the ventricular tachycardia counters to zero and can potentially delay therapy. Programming a higher value of stability (i. e., allowing less stable intervals to be classified stable) can result in therapy delivery for atrial fibrillation, while programming a lower value may result in inhibition of therapy for ventricular tachycardias which may be slightly unstable. The recommended default setting for single-chamber ICDs is 40 ms or 12 % for newer generation ICDs. [20, Rank 3]

Sudden Onset is a detection enhancement that can help to determine whether a tachyarrhythmia is of ventricular or supraventricular origin. Spontaneous ventricular tachycardias typically demonstrate a sudden increase in ventricular rate, while sinus tachycardias increase the ventricular rate slowly over time. Sudden onset is programmed to a default value of 20 % and is available in both VT1 and VT2 zones. This Onset algorithm is designed in order to prevent single fast events as extra beats to fulfill Onset and potentially lead to inappropriate therapy. Onset applies to the ventricular chamber only. Once Onset is fulfilled, it is declared for the entire episode, including redetection. It can be reset by five consecutive intervals that are out of any VT/VF zones with therapy. [21, Rank 5]

An additional detection enhancement based on changes in the QRS morphology is available when using ventricular-only detection for ventricular tachycardia. The QRS morphology is analyzed in a 250 ms window around the peak of QRS in the far-field EGM. This MorphMatch algorithm is based on beat-to-beat analysis of the QRS peak amplitude, the QRS area, and four major QRS deflections. The difference to the reference is calculated for every single beat after alignment of the actual beat to the reference QRS. Normal beats continuously update the reference QRS and an average variability of normal beats is calculated. This average variability (i. e., mean difference to the reference) plus a programmable safety margin result in a morphology threshold to declare a QRS

complex as abnormal (e. g., VT) or normal (e. g., SVT). The Morph Match criterion can be programmed active or inactive. [22, Rank 4]

In parallel to the ventricular tachycardia counter a Morph Match counter increments if the QRS morphology is classified as abnormal. With Morph Match active an episode is declared as ventricular tachycardia when the ventricular tachycardia detection count is met, stability and onset are fulfilled, and at least 50 % of the QRS complexes have an abnormal morphology according to Morph Match. If less than 50 % of the QRS complexes have an abnormal morphology according to MorphMatch this episode is declared as Supra ventricular tachycardia. [23, Rank 4]

Mapping during Ventricular Tachycardia

There have been rapid advances in the field of ventricular arrhythmia therapy over the past two decades following the seminal studies characterising post-infarction Ventricular Tachycardia substrates during cardiac surgery. Activation mapping is now utilised to locate the point of the earliest activation of tachycardia, with entrainment subsequently performed to not only confirm re-entry as the arrhythmia mechanism but to allow for accurate delineation of the critical components of a circuit. The main target for ablation being the central isthmus, represented by mid-diastolic potentials during Ventricular Tachycardia and specific entrainment criteria. [6, Rank 4]

Electro-anatomical mapping and advances in catheter technology have made Ventricular Tachycardia ablation procedures routine in tertiary centres, particularly in post-infarction Ventricular Tachycardia where arrhythmias are more amenable to these activation and entrainment mapping strategies. Indeed, elegant mechanistic studies have identified the role of border zone ultrastructure, scar geometry and anisotropy in determining wavefront curvature and functional block critical to initiate re-entry. Research showed that infarct scar geometric features can be utilised to localise Ventricular Tachycardia isthmuses, and sites of slow stable conduction lie in close proximity to sites of functional block. These principles have been applied clinically in post-infarction Ventricular Tachycardia and recently utilised to define pro-arrhythmic areas based on electrogram morphology and stability. However, in non-ischaemic cardiomyopathy, specific features of the substrate (e.g., myocyte disarray promoting anisotropy in hypertrophic

cardiomyopathy or disruption of myocyte electro-mechanical coupling by desmosomal mutations in arrhythmogenic cardiomyopathy) create functional changes in the tissue to promote conduction block and re-entry. Furthermore, the scar is often very diffuse, making simple delineation of border zones seen in post-infarction Ventricular Tachycardia challenging to define for substrate modification in these disorders.

Therefore, functional changes independent of fibrosis might play an important role in ventricular arrhythmogenesis. This means that ablation relying on identifying fibrotic regions as potential Ventricular Tachycardia isthmuses is probably inadequate, especially since it is assumed that the mechanism of Ventricular Tachycardia involves a critical isthmus, but it is also possible that micro re-entry in an adjacent site is the primary driver with a bystander isthmus. Such sites will elude

conventional ablation catheter bipolar mapping due to lack of resolution, but could be defined in tachycardia with higher-density mapping catheters (e.g., Penta Ray or Orion basket); the functional and structural features of these sites can be dissected. This would explain the lower success rates of ablation in dilated cardiomyopathy versus post-MI Ventricular

“Activation maps are just a visual representation of these activation numbers at various layers of the network as a given image progresses through as a result of various linear algebraic operations. Activation maps are just a visual representation of these activation numbers at various layers of the network.”

Tachycardia, as the mechanism has not been defined or the circuit eludes conventional ablation catheter mapping. [7, Rank 3]

As a result, extensive endo-epicardial ablation and ‘scar homogenis ation’ are frequently performed to modify potentially-arrhythmogenic sites with limited functional analysis. Furthermore, in cardiomyopathy patients, diffuse areas of epicardial fibrosis act as potential re-entry sites, but the arrhythmias are often unmappable because they are haemodynamically unstable or not sustained. A deeper understanding of mechanisms of Ventricular Tachycardia in these cases (i.e., micro re-entry, functional block leading to isthmus formation, repetitive Purkinje activity, the interplay between structural inhomogeneities and dynamic conduction–repolarisation interactions) is required to optimise therapeutic targeting and risk

stratification in Ventricular Tachycardia.

A major limitation of mapping during Ventricular Tachycardia is haemodynamic intolerance of the arrhythmia, with as few as 10 % of arrhythmias induced being stable. Advances in interventional cardiology have led to smaller infarct sizes and Ventricular Tachycardia with shorter cycle lengths accounting for the decreasing use of mapping during tachycardia due to their haemodynamic instability or transient nature. The obstacle posed by unstable Ventricular Tachycardias could be addressed using haemodynamic support devices. Percutaneous left ventricular assist devices allow more detailed and prolonged mapping of unstable Ventricular Tachycardias with more Ventricular Tachycardia terminated by ablation, although no impact on the inducibility of Ventricular Tachycardia at the end of procedures is evident. Whether these disappointing results are due to selection bias needs to be analysed in further trails. Extracorporeal membrane oxygenation has also been studied in this context. Its use allows for mapping, ablation and subsequent non-inducibility of Ventricular Tachycardia that were previously inducible at the end of substrate-based approaches. [8, Rank 2]

On a practical level, although entrainment mapping is seen by many as the gold standard for the interrogation of a re-entrant circuit, it also suffers limitations that stretch beyond the afore-mentioned haemodynamic issues. Problems include inability to capture or having to increase pacing outputs, which increase the volume of captured tissue leading to inaccuracies in defining the exact site of the isthmus, as the captured area can be over 2 cm away. Even if consistent capture is achieved, oscillations in the tachycardia cycle length can introduce errors, resulting in misleading post-pacing intervals or local tissue properties causing latency and long return cycle lengths, appearing as bystander sites. These confounding issues might only become apparent after ablation has not terminated the tachycardia. Finally, due to the muscular bundles that form the isthmus being only a few hundred microns in diameter, the diastolic component can be very low in amplitude and difficult to detect, especially if the noise levels in the catheter laboratory are high and mapping system filters saturated at specific frequencies. [9, Rank 1]

Substrate Mapping

Due to limitations, and the fact that patients can have multiple haemo-dynamically unstable or non-sustained VT, substrate mapping and ablation have gained popularity. During sinus rhythm mapping,

low-amplitude, fractionated electrograms and late potentials associated with surviving bundles of myocardial tissue surrounded by fibrous tissue are identified. Early work employing sub-endocardial surgical resection of these areas eliminated approximately 50 % of the abnormal signals and reduced Ventricular Tachycardia recurrence. Homogenisation of scars, involving ablation of these abnormal potentials within scars, reduces Ventricular Tachycardia recurrence in patients with ischaemic cardiomyopathy. Translation of these results to non-ischaemic cardiomyopathy is difficult, with outcome measures less impressive than with ischaemic cohorts. [10, Rank 3]

Extensive ablation of local abnormal ventricular activities has also been demonstrated to significantly reduce Ventricular Tachycardia recurrences in secondary prevention cases, but extensive ablation is required with long procedure times of up to 186 +/–78 minutes. This highlights the question of how much ablation is truly required to prevent recurrences. As such, there is no universal agreement on optimal ablation strategy for scar substrate. Randomised trials examining substrate-based ablation exist in the form of the ablation of clinical ventricular tachycardia versus addition of substrate ablation on the long term success rate of VT ablation (VISTA) and the substrate mapping and ablation in sinus rhythm to halt ventricular tachycardia (SMASH-VT) trials. The VISTA trial demonstrated that an extensive substrate-based approach was superior to a more focused activation mapping strategy. For obvious reasons, only tolerated Ventricular Tachycardia was included in the activation mapping arm, and whether these results can be extrapolated to the wider Ventricular Tachycardia cohort of patients is unclear. The randomised, primary-prevention trial, SMASH Ventricular Tachycardia, showed a reduction in Ventricular Tachycardia events using a substrate-based approach. The positive results of this trial, which achieved a 70 % reduction in arrhythmic events at 2 years, has not been replicated.

There are many reasons that could explain why the results have been disappointing. Voltage mapping using standard parameters of >1.5 mV as normal tissue and <0.5 mV as scar tissue might lead to underestimation of the heterogeneity of the tissue mapped. The use of bipolar voltage to locate islands of surviving myocardium that could form conducting channels supporting Ventricular Tachycardia is limited by the current technologies employed, primarily 3.5-mm bipolar ablation catheters.

Using smaller electrode sizes with closer bipolar spacing to minimise far-field potentials can increase resolution, and has been to shown delineate areas of surviving myocardium that were labelled as inert scars on maps produced with larger electrodes (e.g., using multipolar Penta-Ray and duodecapolar catheters). Electrode spacing is not the only potential source of error when attempting to delineate scars. The angle at which the catheter is placed on the muscle can lead to falsely low bipolar voltage if it too steep, as the electrodes are activated simultaneously and signal cancellation occurs. [11, Rank 4]

Wavefront direction is another source of error, with late potentials present during apical pacing disappearing during ectopic beats. This phenomenon is also seen when comparing maps created during sinus rhythm and during right ventricle pacing. Sinus rhythm maps show larger scar areas with less late potential. Similarly, differential pacing sites during mapping impact voltage maps created. With the characterisation of scars being different, especially in septal locations and areas of low density, the sensitivity of voltage maps could be improved by using separate pacing locations during mapping. Furthermore, isthmuses present during Ventricular Tachycardia might be absent when mapping in sinus rhythm. The concept of block being functional rather than anatomical has been shown in computer models of Ventricular Tachycardia and in clinical studies. In essence, dynamic changes in conduction-repolarisation lead to transient lines of block, which are cycle-length dependent, creating the opportunity of re-entry to develop at a site. Mechanistically, tissue susceptibility to re-entry depends on the spatial interaction between refractoriness and conduction dynamics, as re-entry requires that a wavefront of excitation finds electrically-excitable tissue always ahead of it. Favourable conditions for re-entry might be met when conduction velocity is slowed by a premature beat and where short repolarisation allows the tissue to regain excitability, therefore potentially enabling the establishment of a re-entrant circuit. A metric to quantify tissue susceptibility to re-entry and predict critical sites for Ventricular Tachycardia initiation based on this principle has recently been proposed. [12, Rank 5]

Localising a Ventricular Tachycardia exit site is often attempted during ablation using the 12-lead electrocardiogram (ECG). These sites can be paced during sinus rhythm and compared morphologically to 12-lead ECGs, with most modern mapping systems containing

software to produce a degree of match between the two. Due to the prevalence of ICDs in the patient cohort, a 12-lead ECG of the clinical Ventricular Tachycardia is rarely captured, and the cycle length of the tachycardia stored on an ICD is often used to identify whether an induced Ventricular Tachycardia is likely to be clinical. Despite the lack of a pre-procedural ECG, Ventricular Tachycardia induced during the case can be used to guide the operator to potential areas of interest. In idiopathic Ventricular Tachycardia,the 12-lead ECG can localise anatomical regions where a Ventricular Tachycardia exit site is most likely to be present. While similar algorithms have been used with some success in patients with structurally-abnormal hearts, the applicability of facets of these algorithms is questionable. In an invasive non-contact mapping study, the use of concordance in the precordial leads was not found to be useful in infarct-related Ventricular Tachycardia. Furthermore, algorithms to assess for epicardial exit sites, which would be useful in preprocedural planning, have proved inaccurate. Pacing in sinus rhythm from sites of concealed entrainment produces unmatched pace maps in just under one-third of cases. Proposed mechanisms underlying the limitations of pace mapping include differential areas of block present during sinus rhythm and Ventricular Tachycardia resulting in different QRS morphologies, and different pacing outputs resulting in divergent myocardial capture. Despite these issues, the utilisation of pace mapping to locate, and subsequently ablate, scar areas with multiple exit sites has been shown to improve Ventricular Tachycardia -free survival in a single-centre study; the implication being the potential to deliver more targeted ablation lesions in regions more likely to support Ventricular Tachycardia. [13, Rank 4]

End Points for VT Ablation

Traditional focus is on the labelling of clinical and non-clinical Ventricular Tachycardia occurring during ablation. Clinical Ventricular Tachycardia being denoted as such if it is similar to the 12-lead ECG, the cycle length recorded from an ICD or occurs spontaneously during mapping. However, arrhythmias labelled as non-clinical might in fact occur spontaneously in the out-of-hospital setting. Studies have differed in their approaches to these distinct re-entrant circuits. Using programmed electrical stimulation at the end of a procedure, some focus only on the clinical Ventricular Tachycardia and others have included non-clinical Ventricular

Tachycardia for their non-inducibility endpoints. Guideline consensus states that non-inducibility of clinical Ventricular Tachycardia in response to programmed electrical stimulation should be considered the minimum endpoint after ablation. Research found that non-inducibility of all Ventricular Tachycardias was associated with significantly lower cardiac mortality. Others have shown inducibility of non-clinical Ventricular Tachycardia to be associated with recurrence. With no available studies specifically designed to address the question of optimal endpoints, it is difficult to produce standardised outcome measures.

The recent increased use of substrate homogenisation necessitates a standardised method for assessing whether all targeted late potentials have been successfully ablated. Scar remapping is one suggested method of assessment, and with more expedient mapping, technologies might become more commonplace. Lack of capture with high-output pacing has been used in addition to late potential abolition as an endpoint. [14, Rank 5]

Major complications occur in approximately 8–10 % of Ventricular Tachycardia ablation procedures, with lower mortality. The three main complications are vascular injury, stroke and cardiac tamponade. In a large, single-centre study of both idiopathic Ventricular Tachycardia and structurally-abnormal heart Ventricular Tachycardia, access-site vascular injury was the most frequent complication at 3.6 %, with stroke and tamponade both <1 %. The incidence of vascular complication might be higher in ischaemic heart disease cohorts, and although the incidence of stroke is low, the use of irrigated catheters is also purported to reduce the risk of stroke further by preventing coagulum formation on catheter tips. Anticoagulation during ablation is achieved with intravenous heparin, and post-ablation anticoagulation is recommended for 6–12 weeks with either aspirin or warfarin. [15, Rank 4]

Tachycardia Management

Ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) accounts for 25 to 36% of witnessed cardiac arrests at home and 38 to 79% of witnessed cardiac arrests in public. Ventricular arrhythmias (VAs) represent a broad spectrum spanning single ectopic beats to sustained Ventricular Tachycardia and Ventricular fibrillation. These arrhythmias encompass clinical conditions ranging from benign to life threatening. Sustained Ventricular arrhythmias are mostly associated with structural

or ischemic heart disease (60 to 80%) followed by channelopathies and idiopathic Ventricular arrhythmias. (Ventricular arrhythmia in the absence of structural heart disease). Although life-threatening Ventricular arrhythmia are greatest in those with known coronary artery disease, myocardial infarction, and depressed ejection fraction, a considerable number of patients with non-ischemic cardiomyopathy (NICM) experience fatal events due to Ventricular Tachycardia or VF as well

Different forms of Ventricular arrhythmia can coexist in the same patient, can be isolated or frequent, and have differing mechanisms. Premature ventricular contractions are the most common and are generally considered benign. Non-sustained Ventricular Tachycardia is at least three consecutive ventricular beats at a rate of at least 100 beats per minute; if ventricular tachycardia exceeds 30 seconds or is hemodynamically unstable; it is considered "sustained". Ventricular Tachycardia can be regular or irregular in rate and morphology. Sustained monomorphic Ventricular Tachycardia has the same activation sequence from beat to beat and generally occurs because of a stable re-entry circuit in patients with structural heart disease or because of automaticity in idiopathic Ventricular Tachycardias. The 12-lead electro cardiogram (ECG) provides an approximation of the exit site. On the other hand, polymorphic ventricular tachycardia that often degenerates into Ventricular fibrillation is more often seen in acute myocardial ischemia or infarction as well as with several genetically mediated syndromes. [25, Rank 5]

The goals of management of Ventricular arrhythmia include symptom relief (including syncope, worsening heart failure, and ischemic chest pain), improving quality of life, and reducing implantable cardioverter defibrillator (ICD) shocks, preventing deterioration of left ventricular function, reducing risk of arrhythmic death, and improving overall survival. Treatment of Ventricular arrhythmia should take into account the underlying medical conditions, the cardiac disorders, the presence of heart failure, the cause for the arrhythmias, consequences of the Ventricular arrhythmias, and the risks and benefits of the therapeutic pharmacological or invasive strategy.

ICDs are the mainstay of therapy to reduce the risk of sudden cardiac death due to Ventricular Tachycardia and ventricular fibrillation. Despite the mortality benefit gained from implantable cardioverter defibrillator therapy, electrical shocks from the device as well as unopposed and

unnecessary right ventricular pacing should be monitored for and appropriately addressed. According to current data, both anti-arrhythmic drugs and catheter ablation may reduce the recurrence of Ventricular arrhythmias without offering any survival benefit. Recurrent ventricular tachyarrhythmias and implantable cardioverter defibrillator shocks are the major indication for anti-arrhythmic drug therapy, but these medications can also be pro-arrhythmic. Catheter ablation has evolved as a promising therapy to reduce the risk of Ventricular Tachycardia recurrence; it is superior to medical therapy alone, according to clinical trials. Despite improved mechanistic understanding and progress in catheter ablation technology that has led to effective treatment of focal and idiopathic Ventricular Tachycardia, the long-term success rates for Ventricular Tachycardia ablation remain modest in both ischemic and non-ischemic cardiomyopathies.

Considerable research and clinical effort in recent years have been focused on the development of diagnostic modalities and imaging tools to identify the arrhythmogenic substrate responsible for VT (focal or scar), genetic screening for markers of channelopathies, and superior mapping and ablation technologies. These advances have allowed us to tailor our approach to Ventricular arrhythmias management on the basis of the underlying etiology with higher efficacy. [26, Rank 4]

Medical Management of Tachycardia

Pharmacologic therapy for preventing Ventricular arrhythmias has yielded disappointing results in recent years. Therapy has been limited because of variable efficacy, pro-arrhythmic effects, patient compliance, and adverse effects from long-term therapy. As adjuvant suppressive therapy in patients with implantable cardioverter defibrillator, amiodarone and sotalol have been shown to reduce the rate of recurrent VT (71% and 15–44%, respectively) when compared with beta-blockers or placebo. Current guidelines recommend pharmacologic therapy (amiodarone or sotalol) with or without adjunctive catheter ablation to prevent VT/VF recurrence and reducing ICD shocks.

Intravenous amiodarone and sodium channel blockers (lidocaine and procainamide) remain the preferred drug regimen in the acute setting; however, more recently, intravenous sotalol has been shown to terminate sustained Ventricular Tachycardia acutely with a higher efficacy versus lidocaine. Neither amiodarone nor

lidocaine, however, has been shown to improve survival or neurologic outcomes in patients with pulseless VT/VF and out-of-hospital cardiac arrest. In the first prospective randomized study comparing intravenous procainamide and amiodarone in the acute treatment of hemodynamically tolerated wide complex tachycardia (VAs), procainamide was shown to be more efficacious in tachycardia termination (67% versus 38%) and was associated with fewer major cardiovascular events (9% versus 41%). The effect was consistently observed even in those with structural heart disease as well as when adjusted for age and sex. [20, Rank 4]

Investigators of the VANISH trial showed an improved composite primary outcome of death, VT storm, or appropriate implantable cardioverter defibrillator shocks among patients undergoing catheter ablation versus escalation of anti-arrhythmic drug therapy (amiodarone or mexiletine or both) but with no significant difference between groups in terms of mortality. In a recent meta-analysis comparing the effectiveness of anti-arrhythmic drugs versus catheter ablation for preventing recurrent Ventricular Tachycardia in patients with implantable cardioverter defibrillator, there was no significant difference between the two treatment modalities (odds ratio (OR) 0.58, 95% confidence interval (CI) 0.26–1.2, P = 0.17) in terms of risk reduction of VT as well as all-cause mortality (OR 0.58, 95% CI 0.24–1.24, P = 0.23). To avoid potential long-term adverse effects and reduce mortality, amiodarone may be safely reduced or discontinued after successful Ventricular Tachycardia ablation without an increase in Ventricular Tachycardia recurrence. Nifekalant, a pure potassium channel blocker that has been approved for use, has not been shown to be superior to amiodarone in treating out-of-hospital cardiac arrest or shock-resistant sustained VT/VF. [21, Rank 3]

Role of ICDs

In epidemiological studies, sudden death is typically defined as unexpected death that occurs immediately or within 1 hour of an abrupt change from a stable clinical state. Sudden death is frequently due to Ventricular Tachycardia degenerating to VF. Numerous risk factors for sudden cardiac death have been identified. It is more than twice as likely in men as in women and more then 3 to 5 times as likely in the setting of structural heart disease, particularly coronary artery disease. Greater than two-thirds of sudden cardiac arrests

are associated with coronary artery disease. It can be the first manifestation of coronary artery disease, making detection of high-risk patients problematic.

Patients who survive a myocardial infarction (MI) are at risk, with the incidence of sudden death or cardiac arrest being highest (1.40% per month) in the first month after MI and decreasing to 0.14% per month at 2 years after MI. One of the most easily identified and most commonly used noninvasive risk factors for sudden death is a depressed left ventricular ejection fraction (LVEF). An LVEF of 30% or less is associated with an annual overall mortality rate approaching 10%. Other risk factors for sudden death include abnormal heart rate variability, microvolt T-wave alternans, and ambient ventricular arrhythmias. Although these noninvasive risk factors have been shown to be associated with an increased incidence of sudden cardiac death in selected patient populations, their usefulness in selecting which patients would benefit from an implantable cardioverter-defibrillator (ICD) remains questionable and is still under study. Inducible Ventricular Tachycardia during invasive electrophysiological study with programmed ventricular stimulation is also a risk factor for sudden cardiac death in patients with ischemic heart disease, for which an ICD is usually warranted. [27, Rank 4]

Patients with depressed ventricular function from cardiomyopathies, congenital heart disease, and valvular heart disease are also at risk of Ventricular Tachycardia and sudden death. Risk factors are less well defined in these populations than for populations with coronary artery disease. Although development of large areas of ventricular scar is not common in non-ischemic cardiomyopathies, sustained Ventricular Tachycardia often seems to be related to a scar that can be identified as areas of delayed gadolinium enhancement on cardiac magnetic resonance imaging. Whether magnetic resonance imaging will be helpful in identifying patients at risk is an area of active interest and is under investigation.

A small but important fraction of sudden deaths are due to genetic causes of cardiomyopathy (hypertrophic or dilated) or to ion channel abnormalities (eg, long QT syndrome, short QT syndrome, Brugada syndrome). A family history of sudden death should prompt careful consideration for these entities. Interestingly, a familial predisposition to sudden death in patients at risk of coronary artery disease has also been shown; a genetic susceptibility to VF during ischemia is one of the hypotheses invoked to explain this observation. [28, Rank 3]

Detection Criteria Associated with ICD therapy

ATP One-Shot

ATP One-shot is a feature that delivers a single ATP therapy for a stable rhythm in the ventricular fibrillation zone prior to shock charging. The rhythm in the ventricular fibrillation zone must be regular (i. e., within 12 % stability), such as a stable fast monomorphic ventricular tachycardia. There is no rate limit for ATP One-shot. Once the ATP is delivered, charging of the capacitors begins automatically. During charging, the device continues to classify the rhythm and charging is aborted once three long intervals (out of four) occur. ATP One-shot is automatically disabled after four consecutive unsuccessful attempts. When the device is interrogated, ATP One-shot will be automatically re-enabled. After analyzing the episodes, the user can decide to deactivate this therapy option. [24, Rank 3]

Non-committed Shocks

Rhythm classification continues through the charging period when shock confirmation is programmed to ON. If the device detects during charge three out of four slow events (i. e., sinus or paced), then the device aborts shock therapy. If self-termination occurs or no further VT/VF intervals are available to synchronize the shock, then the shock delivery will be withheld. The device then begins the redetection/termination process. The aborted shock energy is slowly released into an internal resistor and may make up to 10 min to bleed off. If charging ends, a 70 ms blanking interval is started to avoid oversensing of artefacts due to the switch of high voltage. The shock energy is delivered 30 ms after the next VT/VF interval. [25, Rank 4]

Confirmation applies to all shocks within the programmed ventricular tachycardia or ventricular fibrillation zone. With confirmation programmed ON, the first shock in the detected ventricular tachyarrhythmia zone is non-committed. Each time a shock is aborted, the next shock after redetection is automatically committed. The device will not allow two aborted shocks in a row to occur. This is a safety feature, should intermittent under sensing of a ventricular tachyarrhythmia be present, to prevent therapy inhibition. [26, Rank 3]

Committed Shocks

A committed shock is a shock delivered after (re-)detection and charge. There is no attempt to recheck or verify the

rhythm prior to shock delivery. The device tries to synchronize with the first ventricular sensed or paced event. However, if synchronization is not possible, the device delivers the shock asynchronously within two seconds. [27, Rank 5]

Termination Detection

Termination of a ventricular tachyarrhythmia episode is based on a nonprogrammable 12 out of 16 termination criterion. Termination of an episode is declared when twelve out of a sliding window of 16 intervals are longer (i. e., the rate is slower) than the lowest programmed cutoff interval/ rate limit with therapy. This includes also postshock and antibradycardia pacing intervals. If 12 long intervals are measured before the first window of 16 intervals, termination is declared with the twelfth interval. If detection starts anew following termination, all programmed therapy is available for treatment. [28, Rank 3]

Implantable cardioverter defibrillators effectively terminate VT and VF for most patients and reduce mortality in selected patients at risk of sudden death. Appropriate selection of patients for ICD therapy has been the subject of extensive investigation. Two broad categories of patients are candidates for ICD therapy: those receiving an ICD for secondary prevention of sudden death after surviving an episode of cardiac arrest and those treated for primary prevention of sudden death who have not had a prior cardiac arrest or sustained VT.

Patients who have survived a cardiac arrest or who have sustained VT that causes hemodynamic compromise and is not due to a secondary cause (such as acute MI) have a high risk (>40%) of having a recurrent episode of VT or VF in the next 2 years. An ICD for secondary prevention improves survival (31% reduction in mortality in 3 years).

Implantable cardioverter-defibrillators also reduce mortality rates in selected high-risk patients for primary prevention. Sudden death risk is best identified from depressed left ventricular function. The Sudden Death in Heart Failure Trial (SCD-HeFT) enrolled patients with an LVEF (left ventricular ejection raction) of 35% or less due to either ischemic or non-ischemic heart disease who had New York Heart Association class II or III heart failure. At 5 years of follow-up, ICDs reduced mortality compared with amiodarone (28.9% vs 34.1%) or standard medical therapy (28.9% vs 35.8%). Amiodarone was of no benefit compared with standard medical therapy. Meta-analyses further support a survival benefit for ICD therapy in

> "In Cardiology Activation Mapping refers to a system which plots the position of and activation time at a roving mapping catheter assists in identifying the sites of early activation for focal arrhythmias, and, combined with entrainment mapping, appears to be useful in identifying critical isthmuses in complex reentry circuits."

patients with non-ischemic cardiomyopathy. [20, Rank 4]

Although advanced age is not an absolute contraindication to device therapy, comorbidities can have profound effects on expected mortality in elderly patients, and decisions to implant ICDs must be individualized in this group. [21, Rank 5]

Tachy cardiomyopathy

Tachycardia-induced cardiomyopathy is a long-recognized complication of AF, affecting as few as 3% and as many as 25% of patients with atrial tachyarrhythmias. Several mechanisms have been proposed to contribute to tachycardia-induced cardiomyopathy, including decreased density of L-type calcium channels and β-adrenergic receptors, increased intracellular calcium and diastolic contracture, impaired myocardial blood flow due to raised left ventricular diastolic pressure, oxidative stress, and even deleterious polymorphisms in angiotensin converting enzyme.

Once anticoagulation has been initiated and the risk of thrombus has been addressed, sinus rhythm should be restored with cardioversion. Several methods can be used to maintain sinus rhythm; short-term amiodarone (3 months) is often helpful and allows for recovery before deploying a more durable treatment modality such as catheter ablation. Recovery of ventricular function confirms the diagnosis and may take up to 6 weeks. Patients with tachycardia-induced cardiomyopathy have similar outcomes following catheter ablation compared with patients without structural heart disease. [9, Rank 4]

Tachycardia-induced cardiomyopathy may present itself at any age and has been reported as a result of various tachyarrhythmia mechanisms. Incessant supraventricular tachycardia due to atrio-ventricular re-entry by a concealed accessory pathway in a young male. The tachycardia is terminated following adenosine infusion but with almost immediate spontaneous reinitiation. However, more recently Tachycardia-induced cardiomyopathy has also been described as a result of frequent ventricular ectopic beats. This has been

> "Tachycardia-induced cardiomyopathy (TIC) is a disease where prolonged tachycardia (a fast heart rate) or arrhythmia (an irregular heart rhythm) causes an impairment of the myocardium (heart muscle), which can result in heart failure."

explained by the asynergic and inefficient left ventricular contraction of the ectopic beats, which is similar to that reported in patients with left bundle branch block or right ventricular pacing. The resulting abnormal left ventricular torsion may cause disruption and further progression of asynergic left ventricular wall motion.

The diagnosis of Tachycardia-induced cardiomyopathy requires awareness about this condition, as the underlying arrhythmia may not always be apparent. ***It*** should be suspected in patients with structural heart disease and heart failure who suffer from chronic or frequently recurring tachyarrhythmias and in all patients with no other obvious explanation for ventricular dysfunction. The diagnosis of Tachycardia-induced cardiomyopathy in this latter setting can be only confirmed after cardiac function restoration following tachycardia or heart rate control.

Tachy cardiomyopathy

Advances in the treatment of myocardial infarction (MI) have improved survival after ischemic cardiac injury. Post-infarct structural and functional remodelling results in electrophysiologic substrates at risk for monomorphic ventricular tachycardia (MMVT). Characterization of this substrate using a variety of clinical and investigative tools has improved our understanding of MMVT circuits, and has accelerated the development of device and catheter-based therapies aimed at identification and elimination of this arrhythmia. [6, Rank 5]
*Important information for post-test is highlighted in red letters, boxes and

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