

## **ATRIAL TACHYCARDIAS**

### **ATRIAL PREMATURE BEATS**

Atrial premature beats (APBs) are common in the healthy population and their prevalence increases with age, history of cardiovascular disease, physical activity, and BNP levels.<sup>1</sup> In patients investigated for irregular pulse notification (iPhone or Apple Watch) up to 25% had frequent APBs.<sup>2</sup> APBs have long been considered benign. However, accumulating epidemiological and clinical evidence has established that frequent APBs (usually defined as  $\geq 30$  per hour or a median count of more than 2 APBs per hour, or runs of  $\geq 30$  beats, are independently associated with an increased risk of atrial tachycardia and AF, ischemic stroke, heart failure, and all-cause mortality.<sup>3-5</sup> Even APBs recorded on routinely obtained ECGs are significant. In the NIPPON DATA 90 Registry, even one beat of APC recorded on screening was significantly associated with an increased risk of CVD mortality.<sup>6</sup> In the ARIC study, APBs on routinely obtained ECGs were not associated with sudden cardiac death. However, ventricular premature activity was associated with sudden death, and this effect was additive when APCs occurred concurrently.<sup>7</sup> In the NHANES III data, APBs, but not VPBs, on ECG were associated with total and cardiovascular mortality.<sup>8</sup> APBs may also trigger SVT in the presence of a suitable background. Non-conducted APBs are a common cause of unexpected pauses. They can arise anywhere in the atria, including the sinus node.

An APB is characterized by an abnormally shaped atrial depolarization wave which occurs prior to the next anticipated sinus beat. Several electrocardiographic leads may be needed to distinguish the different P wave shape, and in the rare case of sinus node premature beats the P wave will be identical. The post-extrasystolic cycle is typically less than compensatory due to penetration and resetting of the sinus node by the premature depolarization, but suppression of the sinus node automaticity may also occur and result in pauses equal to or longer than the sinus cycle. Intraventricular conduction may be normal or aberrant, whereas the P-R interval is marginally longer than that of normal sinus rhythm due to atrioventricular nodal delay. This especially occurs in the rare case of interpolated APBs which do not depolarize the sinus node and do not affect the sinus rate. Blocked premature beats may masquerade as pauses or bradycardias when P waves are not seen. The T wave of those beats that precede a pause should be carefully inspected to detect any "hidden" premature P wave. Apart from age and cardiovascular disease, other potential causes of APBs are hypertension, pulmonary disease such as bronchial carcinoma and pneumonia, hyperthyroidism, alcohol abuse, illicit drugs, and anxiety states.

**Therapy** is directed towards avoidance or correction of the offending cause. Caffeine in moderate doses is well tolerated.<sup>9</sup> In symptomatic patients, beta blockers are useful. Experimental studies have identified a functional cardiac glutamatergic system in which N-methyl-D-aspartate receptors regulate atrial electrophysiology.<sup>10</sup> Preclinical studies show that N-methyl-D-aspartate receptors are largely confined to the atrial myocardium and regulate atrial electrophysiology.<sup>10</sup> Pharmacological antagonism with memantine has been found to suppress atrial ectopy and tachycardia with a favorable safety profile, despite previous reports of bradycardia and QT prolongation.<sup>11</sup>

## **ATRIAL AND JUNCTIONAL PREMATURE BEATS**

Premature beats probably arise from the AV junction and conduct antegradely to the ventricles and retrogradely to the atria. There are, therefore, inverted retrograde P' (negative in inferior leads and positive in aVR) the timing of which relative to the QRS complex depends on the exact origin of the beat and the conduction times to the atria and the ventricles. The retrograde P may occur immediately before, during or following the QRS complex which itself may display various degrees of aberration. Concealed His bundle extrasystoles may simulate first- or second-degree AV block, but they can also be associated with conduction disease.<sup>12</sup>

## **PHYSIOLOGIC SINUS TACHYCARDIA**

### **Definition**

Sinus tachycardia is defined as a non-paroxysmal increase in sinus rate to more than 100 bpm in keeping with the level of physical, emotional, pathological, or pharmacologic stress.<sup>13, 14</sup>

### **Aetiology and Pathophysiology**

Sinus tachycardia can be found in 2-5% of apparently healthy people, and represents a spectrum of problems from a normal variant to a chronic ongoing autonomic condition to an underlying inflammatory or infectious process, among others.<sup>14</sup> Most common causes are presented in Table 1. Usually, it is due to physiological influences on individual pacemaker cells and from an anatomical shift in the site of origin of atrial depolarization superiorly within the sinus node.

## Diagnosis

In normal sinus rhythm, the P wave on a 12-lead ECG in adults is positive in leads I, II, and aVF and V<sub>3</sub> to V<sub>6</sub>. It is negative in aVR and V<sub>1</sub> and V<sub>2</sub>. In sinus tachycardia P waves have a normal contour, but a larger amplitude may develop, and the wave may become peaked.

## Therapy

Elimination of the offending cause is mandatory.<sup>14</sup> If additional symptomatic treatment is required, beta blockers are the agents of choice, and when contraindicated verapamil or diltiazem may be used.

# INAPPROPRIATE SINUS TACHYCARDIA

## Definition

Inappropriate sinus tachycardia is a fast sinus rhythm (>100 bpm) at rest or minimal activity that is out of proportion with, the level of physical, emotional, pathological, or pharmacologic stress. The syndrome of inappropriate sinus tachycardia is also defined as a sinus heart rate >100 bpm at rest (with a mean 24-hour heart rate >90 bpm not due to primary causes) and is associated with distressing symptoms of palpitations.<sup>15 16</sup>

## Pathophysiology

The underlying mechanism of IST remains poorly understood and is likely to be multifactorial (dysautonomia, neurohormonal dysregulation, intrinsic sinus node hyperactivity). A gain of function mutation of the pacemaker hyperpolarization-activated cyclic nucleotide-gated (*HCN*) 4 channel has been reported in a familial form of IST.<sup>17</sup> There is also evolving evidence that IgG anti- $\beta$  receptor antibodies are found in IST.<sup>18</sup>

## Presentation

Mean age of presentation is 38 years and women are mainly affected. Symptoms may vary from palpitations (or even no symptoms at all) to presyncope. The prognosis of IST is generally considered benign<sup>19</sup>, and the arrhythmia has not been associated with tachycardia-induced cardiomyopathy in patients with long-standing IST.

## Diagnosis

It is based on:

1. The presence of a persistent sinus tachycardia, 100 bpm at rest or >90 bpm on average over 24 h, during the day with excessive rate increase in response to activity and nocturnal normalization of rate.
2. The tachycardia (and symptoms) is usually nonparoxysmal with P-wave morphology and endocardial activation identical to sinus rhythm.
3. Exclusion of a secondary systemic cause (eg, hyperthyroidism, physical deconditioning), and postural orthostatic tachycardia syndrome (POTS). In POTS there is an increase in heart rate of  $\geq 30$  bpm when moving from a recumbent to a standing position held for more than 30 sec (or  $\geq 40$  bpm in individuals 12-19 years), in the absence of orthostatic hypotension ( $>20$  mmHg drop in systolic blood pressure).<sup>15, 20</sup>

A complete history, physical examination, and 12-lead ECG as well as complete blood counts and thyroid function studies are mandatory, whereas ECG ambulatory monitoring, further biochemistry, treadmill exercise and autonomic testing are optional.<sup>15</sup>

## Therapy

Reassurance and lifestyle interventions such as exercise training, volume expansion, and avoidance of cardiac stimulants should be tried prior to drug treatment (Table 2 and Figure 1).<sup>16, 21, 22</sup> Beta-blockers are useful, but may be needed at doses high enough to cause intolerable side effects. Non-dihydropyridine calcium-channel blockers may also be used but at doses that may cause hypotension, and the evidence regarding these agents is limited.<sup>16, 23</sup> Ivabradine, a selective blocker of the “pacemaker current” ( $I_f$ ) in sinoatrial myocytes that directly slows the heart rate, has been found safe and effective in several small trials<sup>24-27</sup>. However, blockade of the  $I_f$  may perturb the feedback loop underlying baroreceptor control of autonomic balance, thereby increasing sympathetic activity to the heart.<sup>28</sup> It should be preferably co-administered with a beta blocker when possible; this combination may also be more beneficial than each drug alone for IST<sup>29</sup>. Ivabradine should not be taken during pregnancy and breastfeeding.<sup>30</sup> As a substrate of CYP3A4, ivabradine should be avoided or used with caution with concomitant administration of CYP4A inhibitors (ketoconazole, verapamil, diltiazem, clarithromycin, grapefruit juice) or inducers (rifampin, carbamazepine).<sup>31</sup> Catheter modification of the sinus node is moderately effective (60%) but the benefits may be short-term and can be complicated by the need of permanent pacing in 10% of the patients.<sup>32, 33</sup> Narrowing of the SVC and phrenic nerve palsy may also occur.

## **SINUS NODAL REENTRANT TACHYCARDIA**

### **Definition**

Sinus node reentrant tachycardia arises from a re-entry circuit involving the sinus node and, in contrast to IST, is characterized by paroxysmal episodes of tachycardia.<sup>34</sup> This uncommon arrhythmia may be associated with paroxysmal symptoms of palpitation, dizziness and light-headedness. On the ECG, the polarity and configuration of the P waves are similar to the configuration of sinus P waves.

### **Diagnosis**

It is based on:

1. The tachycardia is paroxysmal.
2. P-wave morphology is almost identical to sinus rhythm.
3. Endocardial atrial activation is similar to that of sinus rhythm.
4. Induction and/or termination of the arrhythmia occurs with premature atrial stimuli.
5. Termination occurs with vagal maneuvers or adenosine.
6. Induction of the arrhythmia is independent of atrial or AV-nodal conduction time.

### **Therapy**

Vagal maneuvers or adenosine may be used for acute therapy. Verapamil and amiodarone have demonstrated variable success while beta-blockers are often ineffective.<sup>35</sup> Sinus node re-entrant tachycardia may be effectively and safely treated with catheter ablation targeting the site of earliest atrial activation with respect to the P wave (Figure 1). This approach has been shown to be feasible with a good long-term outcome.<sup>36, 37</sup>

## POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME

### Definition

Postural orthostatic tachycardia syndrome (POTS) is defined as a clinical syndrome usually characterized by an increase in heart rate of  $\geq 30$  bpm when standing for more than 30 s (or  $\geq 40$  bpm in individuals 12-19 years), and absence of orthostatic hypotension ( $>20$  mmHg drop in systolic blood pressure).<sup>15, 20</sup> The prevalence of POTS is 0.2%, and represents the most common cause of orthostatic intolerance in the young,<sup>20</sup> with most patients being between 15–25 years old and  $>75\%$  female. Approximately 50% of patients spontaneously recover within 1-3 years.

### Pathophysiology

A number of mechanisms have been described, including autonomic nervous system dysfunction, peripheral autonomic denervation, hypovolaemia, hyperadrenergic stimulation, diabetic neuropathy, deconditioning, anxiety, and hypervigilance.<sup>20, 38, 39</sup>

### Diagnosis

POTS is diagnosed during a 10 min active stand test or head-up tilt test with non-invasive beat-to-beat haemodynamic monitoring. The evaluation of a patient suspected of having POTS should eliminate other causes of sinus tachycardia such as hypovolaemia, anaemia, hyperthyroidism, pulmonary embolus or pheochromocytoma.<sup>20</sup>

### Therapy

Non-pharmacological treatments such as withdrawal of medications that might worsen POTS, such as norepinephrine transport inhibitors, and compression garments are indicated. Patients strongly suspected of having hypovolaemia should drink  $\geq 2$ –3 L of water per day, and dietary salt intake should be increased to  $\sim 10$ –12 g/day, if tolerated.<sup>40</sup> Regular exercise featuring aerobic reconditioning with some resistance training for the thighs is also recommended.<sup>38, 39,</sup>

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Midodrine, 2.5-10 mg tds, has a rapid onset and is administered three times daily during daytime hours as it can cause supine hypertension.<sup>42</sup> Low-dose propranolol (10–20 mg) acutely lowers standing heart rate and improves symptoms in patients with POTS, while higher doses of propranolol are less well tolerated.<sup>43</sup> Long-acting propranolol does not improve the quality of life (QoL) of patients with POTS.<sup>44</sup> Nonselective beta-blockers are preferable because they additionally block epinephrine-mediated  $\beta$ -2-vasodilation, but other

beta-blockers have not been studied. Pyridostigmine, a cholinergic agonist that works by inhibiting acetylcholinesterase, can increase parasympathetic autonomic tone and has a lower risk of hypertension compared with other medications. Potential side effects include abdominal cramping, diarrhea, and muscle cramps.<sup>45, 46</sup> Ivabradine slows sinus rates without impacting blood pressure, and in an open-label study ~60% of patients with POTS had symptomatic improvement<sup>47</sup>. In patients with hyperadrenergic POTS in particular, has been shown to alleviate symptoms and improve QOL.<sup>48</sup> Ivabradine should ideally be administered with concomitant beta-blockers for long-term therapy<sup>28</sup>.

## **FOCAL ATRIA: TACHYCARDIA**

### **Definition**

Focal AT is defined as an organized atrial rhythm  $\geq 100$  bpm initiated from a discrete origin and spreading over both atria in a centrifugal pattern (Figure 2). The ventricular rate varies, depending on AV nodal conduction. In asymptomatic young people (<50 years of age) the prevalence of focal AT has been reported to be as low as 0.34%, with an increased prevalence of 0.46% in symptomatic arrhythmia patients.<sup>49</sup> In patients investigated for irregular pulse notification (iPhone or Apple Watch) up to 25% had frequent AT.<sup>2</sup>

### **Pathophysiology**

Atrial activation originates from a discrete focus (<2 cm in diameter) with centrifugal spread. Focal AT accounts for up to 10% of SVT referred for ablation.<sup>50</sup> The majority of focal atrial tachycardias that occur in substrates without scar or previous incisional atrial lesions are caused by triggered activity,<sup>51</sup> although electroanatomic abnormalities that may be detected in patients with focal AT, are in support of micro-reentry, particularly in the elderly.<sup>52</sup> In childhood, the lack of effectiveness of DC cardioversion suggests abnormal automaticity as the underlying mechanism. Focal is usually not associated with underlying heart disease, and in this case the prognosis is benign unless if tachycardia-induced cardiomyopathy develops.

### **Presentation**

Onset of episodes may occur at any age, from birth to old age. Palpitations are of substantial variation in duration with sudden increases and decreases in rate. There is usually an abrupt onset and termination with bursts of activity. The clinical course is variable and spontaneous remission is common.<sup>49</sup> In patients with paroxysmal AF a wide spectrum of atrial arrhythmias may coexist (Figure 3) and multiple PV foci in multiple veins can be at the origin of AF.

## Diagnosis

The P wave for focal AT is described as distinct with an intervening isoelectric interval, in contrast to a continuous undulation typical of macro-re-entry tachycardia. However, an isoelectric interval may not be identifiable during accelerated heart rates and/or in the presence of atrial disease resulting in slowing of conduction.

Focal AT is characterized by a change in P-wave morphology, and dissociation between the atrium and ventricular response. The foci of focal AT mainly occur along the crista terminalis (>30%), tricuspid annulus and coronary sinus ostium, mitral annulus, perinodal or para-Hisian region, ostia of the pulmonary veins, left-sided septum, and near the aortic coronary cusps. The morphology of P wave may assist in identifying the tachycardia origin.<sup>53</sup>,<sup>54</sup> Foci arising from the superior crista terminalis display a negative or positive-negative P wave in lead V1 or P wave may be indistinguishable from that during sinus rhythm. A positive or negative/positive biphasic P wave in V1, and negative in lead I indicates a left atrial focus, whereas a negative or positive/negative P wave indicates a right atrial focus. CS ostium foci produce P waves negative in the inferior leads and positive in aVL, aVR.

The distinction between focal AT and AVNRT or AVRT can be made by analyzing the R-P relationship on the surface ECG. Typically, focal AT is associated with a long and variable R-P relationship. However, focal AT can show a short R-P relationship at higher rates and increased AV node conduction. Atypical AVNRT and a concealed accessory pathway with slow retrograde conduction may demonstrate a long R-P interval but the R-P interval is typically constant.

The diagnosis of focal AT can only be established with certainty at the electrophysiology laboratory.<sup>55</sup>

## Therapy

### *Acute*

Beta-blockers or calcium-channel blockers may terminate focal ATs or slow the ventricular rate (Table 3, and Figures 4 and 5). Intravenous adenosine may terminate AT (DADs-triggered AT), but the tachycardia may also continue with AV block. Class IA, IC, and III drugs may also be effective, by prolonging refractoriness or suppressing automaticity<sup>56, 57</sup>. Amiodarone may also be used for cardioversion or slowing of the ventricular rate<sup>58</sup>, but in critically ill patients with atrial arrhythmias the efficacy of rate control is unproven<sup>59</sup>. DC cardioversion is usually effective in acutely terminating the tachycardia, irrespective of the mechanism. If the arrhythmia frequently reinitiates, repeating DC cardioversion is unlikely to be appropriate.

### ***Chronic***

Beta-blockers and calcium-channel blockers may be effective <sup>60</sup> (Table 3 and Figures 6 and 7). Class IC drugs may be effective if first line therapy has failed.<sup>56, 61</sup> Ivabradine may also be effective in focal AT. <sup>62, 63</sup> It should be ideally given with a beta blocker. Amiodarone has been tried in the young and paediatric populations,<sup>64, 65</sup> and theoretically should be attractive in patients with impaired LV function. However, its long-term efficacy is limited by its side-effects.

### ***Catheter ablation***

Catheter ablation is the treatment of choice for recurrent focal AT, especially for incessant AT under which conditions tachycardiomyopathy may otherwise ensue <sup>66</sup> (Table 3 and Figures 6 and 7). Distinguishing macro-re-entrant from focal ATs is critical for the ablation strategy. Focal ATs as well as localized/micro-re-entry display a centrifugal activation pattern that spreads throughout the atria. Mapping and ablation of focal ATs is based on determining the earliest activation site. In PV-related AT, focal ablation may be performed but electrical isolation of both the culprit PV along with other PVs may be preferred. Catheter ablation is reported to have a 75–100% success rate.<sup>55, 67</sup>

## **MULTIFOCAL ATRIAL TACHYCARDIA**

### **Definition**

Multifocal atrial tachycardia is an irregular tachycardia characterized by three or more different P-wave morphologies at different rates. Multifocal atrial tachycardia is commonly associated with underlying conditions, including pulmonary disease, pulmonary hypertension, coronary disease, and valvular heart disease, as well as hypomagnesaemia and theophylline therapy, and, in the past, digitalis toxicity<sup>68</sup>.

### **Therapy**

It should mainly address the underlying condition (Table 4). Intravenous magnesium may also be helpful in patients even with normal magnesium levels.<sup>69</sup> Antiarrhythmic medications in general are not helpful in suppressing MAT.<sup>68</sup> Management often involves slowing conduction at the AV node level to control heart rate. Verapamil has been shown to have some efficacy in patients with MAT who do not have ventricular dysfunction, sinus node dysfunction, or AV block.<sup>70, 71</sup> Metoprolol has been found superior to verapamil<sup>72</sup>, and beta-blockers can be used with caution to treat MAT in the absence of respiratory decompensation, sinus node dysfunction, or AV block. In symptomatic and medically refractory cases in

which LV deterioration is seen, AV junction modification may be used for controlling ventricular rate.<sup>73</sup>

## MACRO-REENTRANT ATRIAL TACHYCARDIAS

The mechanism of macroreentrant atrial tachycardia (MRAT) is reentrant activation around a large central obstacle, generally several centimeters in diameter, at least in one of its dimensions. The central obstacle may consist of normal (ie cavotricuspid isthmus-CTI) or abnormal (ie post-operative or post-ablation scar) structures. The obstacle can be fixed, functional or a combination of each. There is no single point of origin of activation, and atrial tissues outside the circuit are activated from various parts of the circuit.<sup>74</sup>

ECGs with continuous regular electrical activity, most commonly but not invariably of the saw-tooth pattern, are mostly due to macro-re-entrant atrial circuits but micro-re-entry is also possible. However, MRATs with a significant part of the activation of the circuit in protected areas may display a focal AT pattern, with discrete P waves.<sup>74</sup> Entrainment mapping is used to delineate the localization of reentrant circuit.<sup>55</sup>

## CAVOTRICUSPID ISTHMUS-DEPENDENT FLUTTER (Typical Flutter)

### Definition and Pathophysiology

Cavotricuspid isthmus (CTI)-dependent flutter represents a macro-re-entry circuit is around the tricuspid annulus using the CTI as a critical passage at the inferior boundary. The crista terminalis and eustachian ridge are the functional posterior barriers, and the tricuspid annulus the anterior barrier. Activation goes downward in the RA free wall, through the CTI, and ascends in the right septum. Activation of the LA is passive. The upper part of the circuit may be anterior or posterior to the superior vena cava. The activation is usually counterclockwise (or anticlockwise) when seen from the apex and the flutter is called **common**, but it may also be clockwise (**reverse** flutter). The most common patterns of CTI-dependent atrial flutter include a tachycardia showing a counterclockwise rotation in the left anterior oblique view around the tricuspid valve (Figure 8). **Counterclockwise (common) isthmus-dependent flutter** is characterized electrocardiographically by dominant negative flutter waves in the inferior leads (“saw-tooth pattern”) and a positive flutter deflection in lead V1 with transition to a negative deflection in lead V6 at rates of 250 to 350 bpm. A less common pattern (10%) involves clockwise rotation around the tricuspid annulus.<sup>74</sup> **Clockwise (reverse) isthmus-**

**dependent flutter** shows the opposite pattern (ie, positive flutter waves in the inferior leads and wide, negative flutter waves in lead V1, transitioning to positive waves in lead V6).

In the majority of patients there is underlying disease such as heart failure, COPD, pneumonia, myocardial ischemia, or cardiac or pulmonary surgery.<sup>75</sup> Old age (>80%) is a strong predisposing factor.<sup>76</sup>

## Presentation

Patients present with sudden onset palpitations, dyspnea or chest pain. More insidious symptoms such as fatigue and worsening of heart failure may also occur. The typical saw-tooth ECG patterns described above may or may not be present. Typical AFL has a strong reproducible anatomical dependence,<sup>77</sup> resulting in the morphological reproducibility of the ECG. However, the described well recognized ECG pattern may be significantly changed when atrial activation has been modified as it is in cardiac surgery involving atrial tissue, after extensive radiofrequency (RF) ablation, or advanced atrial disease.<sup>78, 79</sup> AAD may also modify the typical ECG pattern<sup>80</sup>. In these situations, an atypical ECG for common or reverse AFL does not rule out a circuit of typical flutter using the CTI.<sup>81</sup> Usually there is a 2:1 AV conduction with a resultant ventricular rate of approximately 150 beats/min. Varying block produces an irregular rhythm, whereas 1:1 conduction may lead to hemodynamic instability.

Typical flutter is related to AF in clinical practice with both being associated with similar clinical settings and coexisting in the same patients, AF may trigger AFL, and after typical flutter ablation AF is frequent.<sup>82-84</sup> Typical flutter may also frequently occur in patients treated for AF with class IC drugs or amiodarone. In this case, flutter rate may be reduced to <200 bpm facilitating 1:1 AV conduction. The action of antiarrhythmic drugs on ventricular activation usually results in wide QRS tachycardia.<sup>85-87</sup>

Beyond symptoms associated to high rate and loss of atrial kick, it should be noted that reversible systolic dysfunction and subsequent tachycardiomyopathy is not unusual,<sup>88, 89</sup> and this favours restoration of sinus rhythm or strict rate control.

## Therapy

### Acute

Rate control is necessary when the ventricular rate is high, but this may be difficult to achieve. AV nodal blocking drugs<sup>90-92</sup>, including amiodarone applied mostly in HF or critically ill patients<sup>93, 94</sup>, may be of help, but not infrequently, cardioversion may be necessary (Table 5 and Figures 9 and 10). Recommendations for AF/Flutter with rapid ventricular response are also provided in the Chapter on AF. Dofetilide and ibutilide, pure class III antiarrhythmic drug, are generally effective for interrupting AFL in i.v.

administration (dofetilide may be also given orally for this purpose), while Class IA and IC drugs have little or no effect<sup>95-102</sup>. Class IC antiarrhythmic drugs should not be used in the absence of AV blocking agents because of the risk of slowing atrial rate that may result in 1:1 AV conduction.<sup>103, 104</sup> Amiodarone may not be very effective acutely to re-establish sinus rhythm, but it does help to control the ventricular rate if too fast.<sup>105, 106</sup> Low-energy electrical cardioversion is commonly used with haemodynamic compromise or after failure of previous actions but it could be first choice due to its high efficacy. Electrical cardioversion for AFL is more effective and less energy is required, compared to AF.<sup>107, 108</sup> In the presence of a PPM or ICD, high-rate stimulation can be used to convert flutter, sometimes through AF.<sup>109, 110</sup> If pacing induces AF, this may allow better control of ventricular rate than flutter. Atrial stimulation can also be done with percutaneous endocardial electrodes or from the oesophagus; this is mostly done in paediatrics.<sup>111</sup> Pre-treatment with procainamide may facilitate conversion of atrial flutter by atrial pacing.<sup>112</sup> Data on pre-cardioversion anticoagulation are lacking, but most probably patients should be treated as those with AF.<sup>113</sup>

In some cases, presenting with 2:1 AV block, the diagnosis of AFL may not be obvious on the ECG. In these situations, i.v. adenosine may increase the degree of AV block and reveal the typical ECG pattern. However, adenosine can produce a rebound increase of AV conduction to 1:1, and may also precipitate AF.<sup>114, 115</sup>

### **Chronic**

Rate control is part of the therapeutic approach, using AV nodal blocking agents such as diltiazem, verapamil or beta-blockers (Table 5 and Figures 11 and 12). When ablation is not feasible or the patient's preference, antiarrhythmic drugs may also be used to maintain sinus rhythm. Dofetilide<sup>102</sup> and sotalol<sup>116</sup> are useful but there are concerns about proarrhythmia. Amiodarone may have a role<sup>117</sup>, but it should be restricted to cases of HF or significant structural heart disease.

### **Catheter ablation**

Catheter ablation is the most effective therapy to maintain sinus rhythm, and clearly superior to amiodarone<sup>117, 118</sup>. Upon completion of the ablation line, complete bi-directional block of the cavo-tricuspid isthmus (CTI) should be confirmed to avoid recurrences of the flutter.<sup>119</sup> Ablation of the CTI with validated stable bidirectional conduction block results in <10% recurrences<sup>120</sup>. However, the incidence of AF is high in the long-term.<sup>121</sup> When typical CTI dependent AFL ensues during antiarrhythmic drug therapy (Class IC or amiodarone) for AF, CTI ablation is an acceptable choice to ensure that AAD can be continued for AF control.<sup>117,</sup>

<sup>118</sup>

Although no procedure-related mortality had been detected in previous studies,<sup>122 123</sup> in recent studies mortality of 0.2-0.34%, and stroke rates 0.19-0.5% were reported.<sup>124, 125</sup> In a

recent registry, ablation for flutter had a higher mortality than that for AF (0.3 vs 0.05%) but this might be due to comorbidities or advanced age of patients referred for flutter ablation.<sup>126</sup>

### **Anticoagulation**

Data about the embolic risk of AFL have been usually derived in the presence of concomitant AF, thus making individualized risk stratification difficult. Left atrial appendage “stunning” and thrombi seem to be lower when compared to AF<sup>127, 128</sup>. The thromboembolic risk of AFL, although lower than that of AF<sup>129</sup>, is still significant<sup>130-133</sup>. That, together with the association with AF, justifies thromboprophylaxis and anticoagulation has been recommended as in AF (Figure 13).<sup>13, 134</sup> It should be noted, however, that there is a lack of prospective dedicated randomized studies on the subject. Furthermore, the value of the CHA2DS2-VASc score in preventing ischemic stroke in patients with AFL is not established,<sup>135</sup> and in patients without concomitant AF the threshold for initiation of anticoagulation appears higher than that for patients with AF.<sup>129</sup>

## **OTHER CTI-DEPENDENT FLUTTERS**

An atypical ECG pattern may not exclude CTI-dependent flutter.<sup>136</sup> **Lower-loop re-entry** refers to a circuit rotating around the inferior vena cava instead of around the tricuspid annulus. It may be clockwise or counterclockwise.<sup>137</sup> When rotating counterclockwise it might be considered a variant of typical counterclockwise flutter with a caudal shift of the cranial turning point posterior to the entry of the superior vena cava, resulting in a similar ECG appearance. **Figure-of-8 double-loop reentry** may also occur around the IVC and tricuspid annulus and mimic typical clockwise atrial flutter.<sup>137</sup>

## **NON- CTI-DEPENDENT (ATYPICAL) FLUTTERS**

The terms non-CTI-dependent macro-reentrant atrial tachycardias (MRAT) and atypical flutter are used interchangeably, and describe flutter waves in the ECG not suggestive of typical flutter. However, an atypical ECG appearance can be present when typical circuits develop in diseased atria, most frequently after surgery or extensive ablation, or due to the effects of antiarrhythmic drugs. An EPS is usually required to determine the location of the re-entry circuit. **Upper-loop reentry** may mimic a typical flutter ECG pattern without being CTI-dependent (Figure 20).<sup>136</sup> Atypical atrial flutter/MRAT could also arise from upper loop re-entry in the RA with conduction through the gap in the crista terminalis.<sup>138</sup> **Figure-8 double-loop reentry** tachycardias mimicking the ECG pattern of a common atrial flutter may also occur following surgical atriotomy.<sup>139</sup>

Atypical atrial flutter/MRAT often are scar-related and are fairly common in patients who have undergone extensive left atrial ablation for atrial fibrillation or who have an incisional scar in the right atrium following open heart surgery.

### **Right atrium atypical flutter/MRAT**

Atrial sutures and patches used for complex congenital heart disease surgery together with progressive atrial damage, create multiple obstacles and protected isthmuses that constitute the substrate for complex and multiple MRAT.<sup>140, 141</sup> This usually happens around RA free wall scars. However, in patients with complex congenital heart disease, the presence of extensive atrial scars hinders the differential diagnosis of focal or macroreentrant atrial tachycardias.<sup>142</sup>

Right atrial MRAT may also occur in the absence of previous intervention. Most of these are sustained around areas of “electrical silence” in the RA free wall, probably due to fibrosis<sup>79, 143</sup>.

RF ablation of the critical isthmuses of the reentry circuits is the most effective treatment. Circuits around scars of longitudinal atriotomy can be mapped and ablated with good long-term results.<sup>144</sup>

### **Left atrium atypical flutter/MRAT**

Circuits sustaining LA MRAT are most usually due to electrically silent areas of abnormal tissue following medical interventions or progressive atrial degeneration/fibrosis.<sup>145</sup>

Anatomical obstacles such as the ostia of PVs, and mitral annulus are often involved.

Due to its widespread use, *AF ablation* is the procedure that frequently causes the lesions able to sustain re-entry circuits, usually after linear ablation or extensive defragmentation. Localized segmental PVs disconnection may cause focal tachycardias,<sup>146</sup> and circumferential antral ablation may also create MRAT due to gaps in the lines.<sup>147-151</sup> AT due to a small reentrant circuit after ablation of atrial fibrillation often can be distinguished from macroreentry by a shorter p-wave duration. Right atrial MRATs have a higher incidence of negative P waves in at least 1 precordial lead compared with left atrial macroreentry.<sup>152, 153</sup> Post-AF ablation MRAT can be ablated by deployment of a stable line of block at critical isthmuses.<sup>55</sup> However, intervention to treat these tachycardias after the initial AF ablation should be delayed, if possible, for at least 3 months.<sup>154</sup>

Atrial circuits are also created after *surgery* for different conditions, including mitral valve disease, and are related to incisions or cannulation.<sup>155</sup> Surgery to treat AF may also result in macro-re-entry circuits and focal AT.<sup>156</sup>

Circuits causing atypical left MRAT may also occur in the LA without prior intervention, commonly, but not invariably, associated with significant left heart disease.<sup>157</sup> These are based on areas of electrical silence, probably due to fibrosis, engaging anatomical obstacles such as the ostia of the PVs or the mitral annulus, and may be ablated by

interrupting critical isthmuses.<sup>158</sup> Circuits may also happen in the LA septum due to slow conduction caused by atrial disease or antiarrhythmic drugs.<sup>159</sup>

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