Arrhythmia induced cardiomyopathy secondary to atrial fibrillation: an easy condition to recognise and treat?

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What is arrhythmia induced cardiomyopathy?

Arrhythmia induced cardiomyopathy is a condition characterised by either a tachyarrhythmia (also known as a tachycardia induced cardiomyopathy or tachycardiomyopathy) or frequent ventricular ectopy (also known as ectopy induced cardiomyopathy) that results in left ventricular dysfunction and heart failure. In addition, the dysfunction is partially or completely reversible once control of the tachyarrhythmia or frequent ectopy is achieved.

Key features of an arrhythmia that will result in arrhythmia induced cardiomyopathy (AIC) are: rapid ventricular rates, an irregular rhythm, and asynchronous myocardial contraction, however not all need to be present to result in AIC. The length of time spent in and persistence of the arrhythmia are also important, but have yet to be clearly defined beyond work in animal models. With that in mind, the resistance of the arrhythmia to treatment and the presence (or lack of) symptoms act as risk factors to develop AIC.

Atrial fibrillation (AF) is the commonest cause of AIC and is reported to be present in 10-50% of patients with heart failure. 25-50% of patients with left ventricular dysfunction and AF demonstrate some degree of AIC, however AIC frequently co-exists with other aetiologies of heart failure. There is therefore a pure AIC where the arrhythmia is the only cause of heart failure and an impure one where an arrhythmia worsens and / or exacerbates heart failure of another aetiology.

What is the pathophysiology of AIC?

Animal models have proved useful in understanding AIC using frequent and rapid pacing of the right ventricle, which causes a dilated cardiomyopathy and is reversible once pacing is terminated. The studies have not been able however to clearly define the relative contributions of rate, irregularity and ventricular dyssynchrony in causing heart failure. The proposed pathophysiological cascade has been well described elsewhere. In summary, an arrhythmia in a predisposed individual (of which age, pre-existing myocardial dysfunction and co-morbidity are important) results in energy depletion, ischaemia and oxidative stress at a cellular level. This leads to myocyte dysfunction, neurohormonal activation and abnormal calcium handling, which in the longer term results in the structural and functional changes seen in AIC. Where the dividing line between reversible and irreversible LV dysfunction occurs is unclear, but appears to be time dependent, necessitating earlier diagnosis and intervention.

How do I recognise the patient with AIC?
We are frequently faced with patients in clinical practice who have the combination of AF and heart failure, however teasing out which came first (the old chicken or the egg question) is not easy. A high index of suspicion is therefore required for AIC, particularly given the reversibility of the condition. Useful recommendations for identifying responders include: onset of AF before or at the same time as heart failure, a normal ECG other than the presence of AF, no other cause of heart failure likely (exclusion of ischaemic heart disease, valve disease and alcohol induced cardiomyopathy), and the absence of late gadolium enhancement on cardiac MRI5,7.

In practice, an additional pointer is either: a trial of restoring sinus rhythm with direct current cardioversion (DCCV) or rate control of the AF; and monitoring the response of the left ventricle with serial imaging, with recovery expected within 3-6 months if sinus rhythm or good rate control is maintained8.

How do I manage AIC secondary to AF?

Guideline directed medical therapy of both AF and heart failure with a reduced ejection fraction (HFREF) remains the standard of care with rate control recommended as first line therapy9,10. Evidence from the RACE II trial11 showed no benefit from a lenient versus a strict rate control regime however the study recruited patients with reasonable rate control at baseline (mean 96 beats per minute in both groups) which therefore is unlikely to have included a significant number of those with a tachycardia-induced cardiomyopathy. Given at present we do not fully understand the rate threshold for developing AIC, we equally have no clear target rate to aim for in affected patients. There is also evidence that treatment of rate alone is insufficient to treat AIC, most likely due to the ongoing irregularity of the ventricular response12. Rate control may therefore not be the most appropriate first line therapy in all comers with AIC secondary to AF, particularly in individuals reliant on atrial contraction for ventricular filling (e.g. hypertrophic cardiomyopathy or heart failure with a preserved ejection fraction); and in those who show no improvement despite good rate control that subsequently benefit from a trial of sinus rhythm.

Rhythm control is theoretically preferable in the management of AIC due to targeting both the rate and irregularity of AF. Results from initial randomised control trials (RCT) however were unable to confirm this in practice. The rhythm control versus rate control trial for AF and heart failure (AFCHF)13 is the largest RCT to date, and showed no difference in the primary endpoint (cardiovascular death) or secondary endpoints (all cause mortality, stroke or worsening heart failure). Rhythm control included a combination of anti-arrhythmic drugs (AAD) and DCCV. One possible reason why no difference was seen is that entry was not limited to specific aetiologies of LV dysfunction, therefore the majority had a low probability of having AIC and the potential for reversibility. Another reason is the requirement for long term AAD therapy and their unwanted effects offset any benefit gained from rhythm control.

More recently, a number of smaller studies have been published which have shown benefit from restoration of sinus rhythm through a rhythm control strategy with an improvement in left ventricular ejection fraction (LVEF)14-19, however it should be noted not all have reported positive results20.
This has led to the publication of a number of meta-analyses\textsuperscript{21-23}, which have reported a significant improvement in LVEF in patients who undergo catheter ablation of AF who have symptomatic heart failure and a reduced LVEF at baseline. An important observation from the larger of the two meta-analyses\textsuperscript{22} is that the time to ablation from first episode of AF and diagnosis of heart failure both result in a statistically lower recurrence rates, suggesting timing of rhythm control in AIC is important to prevent irreversible LV remodelling. An alternative explanation is that AIC is more likely when there is a clear deterioration in LVEF within a short time from AF onset compared with those with longstanding AF, who are less likely to have AIC and therefore least likely to benefit from an invasive approach. Catheter ablation does not result in rhythm control in all-comers however, with only around 60% remaining in sinus rhythm at the end of the follow up period (mean follow up just under 2 years). The success of a single procedure is also low with freedom from atrial arrhythmia after a single ablation achieved in around 40%, with the majority going on to need 2 or more procedures to maintain sinus rhythm. The need for repeat procedure is more frequent compared to those without LV dysfunction\textsuperscript{23}, however those with the worst LVEF have the most to gain by restoration of sinus rhythm potentially offsetting the risk of multiple procedures\textsuperscript{24}. When rhythm control is achieved, a number of the individual trials consistently report improvements in NYHA functional class, six minute walk distance (6MWD) and Minnesota living with heart failure questionnaire (MLWHFQ) scores which is supported by the meta-analysis\textsuperscript{21}. Whether this was maintained beyond the short follow up period of, on average, 2 years is unclear, and data on harder endpoints, specifically mortality, is currently lacking.

Not all who entered these trials did receive an improvement in LVEF however. Whether this reflects an inability to correctly recognise AIC or an inability to intervene before irreversible remodelling had occurred is unclear. Another possibility is that AIC is being overdiagnosed and is not as important a clinical entity in the real world as work in animal models suggests, particularly compared to a tachycardia-induced cardiomyopathy alone. There was variation in the entry populations with regard with paroxysmal versus persistent AF, and adequacy of rate control prior to undergoing an ablation making direct comparisons difficult with respect how much benefit is achieved by restoring sinus rhythm over better rate control.

Improvement in LVEF after ablation has also been shown in those who fail to achieve sinus rhythm when a trial of AAD (amiodarone) and DCCV is given first. Bortone et al\textsuperscript{7} reported an improvement in LVEF was achieved after at least 3 months of sinus rhythm after ablation however entry into the trial was stringent selecting those where an AIC was highly likely to be the cause of HFREF. This again suggests the ability to suspect and correctly recognise AIC is essential if patients are to benefit from an invasive approach. The study however was non-randomised, and may simply reflect improved medical care in the ablation group with a natural improvement in LVEF often seen in non-ischaemic cardiomyopathy on guideline-directed medical therapy rather than benefits from ablation itself.

Catheter ablation has also been shown to be superior to atroventricular node ablation and cardiac resynchronisation pacing for improvement in LVEF, 6MWD and MLWHFQ scores in those with drug resistant AF and symptomatic HFREF\textsuperscript{12}. It does therefore hint that in selected groups, rhythm control may be superior to rate control, but the numbers in this trial were low (around forty in each arm) so it would need to be replicated in larger trials before any firm recommendations could be made.
Finally, catheter ablation is also superior to amiodarone in the treatment of AF in patients with symptomatic heart failure. The AATAC-AF trial has shown statistically significant benefits from ablation in: freedom from atrial arrhythmia, improvement in LVEF, 6MWD, MLWHFQ scores, rehospitalisation and all cause mortality. Not only does this suggest catheter ablation should be the first line rhythm control intervention in heart failure, but also why rhythm versus rate control trials using AAD such as AFCHF should be reassessed in the ablation era. The CASTLE AF study looking at the effects of morbidity and mortality from catheter ablation versus medical therapy of AF in LV dysfunction is expected to answer this important question with results expected after 2019.

Until further large scale randomised control trials provide greater insight into the management of AIC with particular reference to hard endpoints of morbidity and mortality, current guideline-directed therapy of good rate control remains the key aim in everyday practice.

Conclusions

In summary, AIC is an important cause of heart failure, not just by itself but also in combination with other aetiologies leading to a worsening of symptoms and LVEF. AF is the commonest arrhythmia responsible for AIC, with growing evidence that rhythm control should be the first line therapy (particularly with catheter ablation) over rate control as recommended in current guidelines. The real difficulty however arises in clinical practice in separating out those with a true AIC, and concomitant AF and HFREF. Recognising the possibility of AIC should alert the clinician to trialling rhythm control therapy first (e.g. amiodarone and DCCV) and assessing response, with a view to a more invasive strategy afterwards. This is particularly important as the benefits of rhythm control seem to be time dependent before irreversible LV remodelling occurs. Despite the poor success rate from a single ablation, the clinician should not be dissuaded from repeat attempts as patients with AIC potentially have the most to gain due to reversibility of LV dysfunction. Whether this selective rhythm control strategy will result in improvements in morbidity and mortality remain to be seen.

References:


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