British Cardiovascular Society

Can we stop treating atrial fibrillation-induced heart failure?

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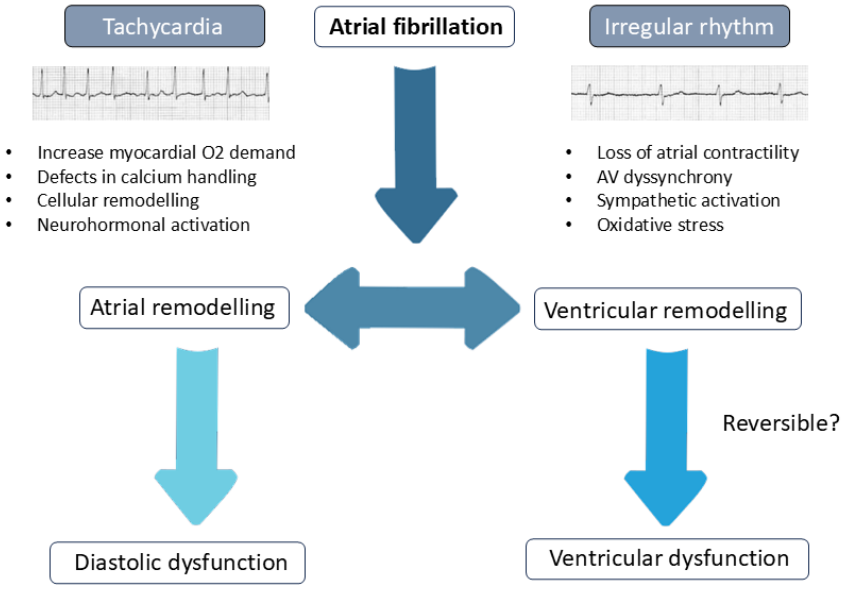
Take Home Messages

- Atrial fibrillation-induced cardiomyopathy may be a reversible process.
- WITHDRAW-AF evaluated stopping heart failure medication after left ventricular recovery in patients with atrial fibrillation-induced cardiomyopathy.
- 5/60 of patients relapsed, defined as a decline in left ventricular function <50% following heart failure medication withdrawal.

Introduction

Approximately 8% of those presenting with an arrhythmia have arrhythmia-induced cardiomyopathy, with atrial fibrillation (AF) being the most common cause. (1, 2) Persistent tachycardia, defined as heart rates >100-110 beats per minute for days to weeks due to AF, can lead to left ventricular (LV) systolic dysfunction. (3) However, AF may also contribute to the development of cardiomyopathy independent of tachycardia (Figure 1). (4)

Figure 1: Pathophysiology of AF-induced cardiomyopathy



Is AF-Induced Cardiomyopathy Reversible?

The CAMERA-MRI trial compared catheter ablation to medical therapy in patients with AF-induced cardiomyopathy and LV ejection fraction (LVEF) <45%. Ablation resulted in a 13.4% improvement in LVEF compared with medical therapy. (5) Subsequently, CASTLE-AF demonstrated that ablation in patients with AF and LVEF <35% reduced all-cause mortality and heart failure (HF) hospitalisations compared with medical therapy (28.5% vs 44.6%). (6) Mean LVEF improved 7% in the ablation group at 12 months. In end-stage HF patients, ablation led to a reduction in death, left ventricular assist device insertion and heart transplantation in the CASTLE-HTX trial. (7) The CRAAFT-HF and DanAblate-HF trials are currently enrolling large numbers of patients to evaluate whether ablation in AF patients with HF is superior to medical therapy. (8,9)

These trials raise an important question: If AF is eliminated and LV function normalises, should HF therapy be continued?

Stopping Heart Failure Treatment – Remission or Recovery?

Potential benefits of withdrawing HF therapy include reducing medication side effects, polypharmacy and the financial burden medications place on patients and healthcare systems. In 2019, the TRED-HF trial evaluated withdrawal of HF therapies in 63 patients with dilated cardiomyopathy. (10) 44% of those in the withdrawal group relapsed after 6 months, with worsening LV function and associated HF symptoms. Swedish HF registry data show withdrawal of ACE inhibitors and mineralocorticoid receptor antagonists are associated with a 38% and 34% increased risk of death or HF hospitalisation, respectively. (11)

These findings suggested that improvement in cardiac function often reflects remission rather than true recovery, particularly when the underlying pathological substrate persists. However, this paradigm might not apply to cardiomyopathies with potentially reversible causes such as AF-induced cardiomyopathy.

WITHDRAW-AF trial

WITHDRAW-AF trial was a multicentre, open-label, randomised controlled trial that evaluated withdrawal of HF therapy following AF rhythm control and LVEF normalisation. (12) Sixty patients

with a prior LVEF <40% secondary to AF whose LVEF had since improved to >50% were randomised. Inclusion criteria required NT-proBNP <250ng/L, absence of late gadolinium enhancement (LGE) on cardiac MRI (CMR), no HF symptoms, treatment with ≥2 HF medications and no AF recurrence in the preceding six months. 97% had undergone AF ablation prior to medication withdrawal. AF recurrence was detected by implantable cardiac device or Kardia.

Table 1: Results of the WITHDRAW-AF trial

	Early-withdrawal N=30	**Delayed-withdrawal N=30**
LVEF pre-withdrawal, %, median	60	60
LVEF post-withdrawal, %, median	58	59
Relapse rate, n (%)	3/30 (10%)	2/30 (6.7%)
AF recurrence, n (%)	13/30 (43%)	13/30 (43%)
Diastolic dysfunction at baseline, n (%)	5/30 (16.7%)	5/30 (16.7%)
Diastolic dysfunction at endpoint, n (%)	2/30 (6.7%)	3/30 (10%)

Abbreviations: Left ventricular ejection fraction (LVEF), Atrial fibrillation (AF)

In the early-withdrawal group, medications were weaned over 12 weeks, followed by six months off therapy. After six months, the delayed-withdrawal group then weaned and stopped their medications. A crossover design was employed so each participant served as their own control to mitigate confounding as patients were not blinded to allocation.

The primary outcome was maintenance of LVEF >50% on CMR at six months. 27 of 30 in the early-withdrawal and 28 of 30 in the delayed-withdrawal group maintained LVEF >50% six months after medication withdrawal. During extended 12-month follow-up, 50 patients who elected to remain off HF therapy remained stable with LVEF >50%. No major adverse cardiac events or deaths occurred during the study. Patients who relapsed had no overt HF symptoms.

Table 2: Characteristics of patients who relapsed		
	Relapse N = 5	**No relapse N = 55**
LVEF at LVSD diagnosis, median	25%	25%
Enrolment LVEF, median	52%	58%
Endpoint LVEF, median	45%	~57–59%
Median no. of HF agents	3	2
AF recurrence, n (%)	1 (20%)	15 (27%)
LGE at 12 months, n (%)	4 (80%)	2 (3.6%)

Abbreviations: Left ventricular ejection fraction (LVEF), Left ventricular systolic dysfunction (LVSD), Heart failure (HF), Atrial fibrillation (AF), Late gadolinium enhancement (LGE).

Analysis

Relapse rates were substantially lower in WITHDRAW-AF than in TRED-HF (8.3% vs. 44%). Investigators used absence of LGE on CMR and temporal association to identify patients with AF-induced cardiomyopathy. However, AF may itself be the consequence of another cardiomyopathic process making temporal association unreliable. Four of the five patients who relapsed went on to develop LGE on repeat CMR, suggesting concurrent non-AF-induced cardiomyopathy. AF recurred in 26 of 60 patients, although AF burden was low. Predicting AF recurrence remains difficult, and recurrence may pose a risk of further LV function deterioration in those off therapy.

Applying this trial to a real-world cohort might be challenging. The study population was highly selected, with only 60 of 139 screened patients randomised. SGLT2 inhibitor use was limited as not widely available at the time of the trial. Additionally, intensified imaging and rhythm monitoring may offset some of the financial and logistical benefits of medication withdrawal.

Follow-up was limited to 12 months. Registry data suggest ongoing improvement in LV function 12 months after initiation of HF therapy (13). But it's unclear how quickly LVEF declines after stopping HF therapy. All relapsing patients had a low-normal EF (50-55%) at randomisation, a range associated with developing HF. (14,15) This may have hinted that their LV function had not completely recovered. Furthermore, there is no clear consensus on how arrhythmia-induced cardiomyopathy should be

defined; (2) the trialists adopted a threshold of LVEF <50%, rather than incorporating a relative decline (e.g., >10% reduction in LVEF), potentially overlooking clinically meaningful deterioration.

Conclusions

The WITHDRAW-AF and TRED-HF trials have demonstrated that HF withdrawal studies can be performed safely under close monitoring. These findings suggest that AF-induced cardiomyopathy may be a reversible process, and that HF therapy withdrawal may be appropriate if truly reversible disease can be reliably identified. Future trials should evaluate HF withdrawal strategies in other potential reversible cardiomyopathies, including peripartum cardiomyopathy and thyrotoxicosis-induced cardiomyopathy.

Disclosures

The author declares no conflicts of interest related to this work.

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