RESEARCH HYPOTHESIS

Heart rate – a novel target for treatment of peripartum cardiomyopathy?

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ABSTRACT

During pregnancy, heart rate (HR) is physiologically elevated but recovery occurs within 4 weeks of delivery. Peripartum cardiomyopathy (PPCM) is an acute condition which manifests with symptoms of heart failure late during pregnancy, or within 6 months of delivery. One of its main symptoms is elevated HR. Current standard therapy for PPCM makes use of diuretics, ACE inhibitors and beta-blockers. This approach does not satisfactorily improve HR in patients, even after 6 months of treatment. Strong evidence from both experimental and clinical studies suggests that modulation of the sino-atrial node with drugs such as ivabradine may benefit patients suffering from PPCM. The activity of ivabradine is likely two-fold – direct with regards to heart rate and indirect with long-term structural changes affecting the heart itself, as well as the vascular and endogenous physiological systems. Large clinical trials are needed to validate this concept and further exploration of this hypothesis in an established rodent model of PPCM is required to investigate the outcome on both HR and its effects on other observable systems affected by PPCM.

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Peripartum Cardiomyopathy (PPCM) is a maternal condition which manifests with symptoms of heart failure between the last month of pregnancy and 5 months postpartum.[1] It is an important health concern in the sub-Saharan region of Africa, with approximately 1 in 1 000 pregnant women affected by the condition in South Africa.[2]

The time course and evolution of the disease is not well understood and the large variability between patients' phenotypes may explain that. Indeed, one main pathophysiological feature of PPCM is left ventricular systolic dysfunction (ejection fraction <45%). However, only a subgroup of patients presents with left ventricular dilatation.[1] The precise mechanism leading to left ventricular dysfunction in human PPCM remains undefined. Several experimental and clinical studies lend support to the hypothesis that increased oxidative stress, as evidenced by increased circulating levels of pro-oxidative factors in PPCM patients, may play an important role in the initiation of the disease.[3,4] Oxidative stress, together with excess anti-angiogenic signaling, leads to vessels rarefication.[5,6] As for diabetic cardiomyopathy,[7] microvascular insufficiency has been suggested to be the driver of PPCM pathogenesis. Endothelial dysfunction and an imbalance of angiogenesis seem to promote metabolic shortage in the heart leading to cardiomyocytes apoptosis,[8,9] further leading to heart failure in PPCM.[10,11]

The rapid cardiac decompensation observed in PPCM patients may be explained by maladaptive remodeling. However, not enough is known about cardiac remodeling in PPCM. The importance of inflammation has been highlighted in animal models and in patients.[6,12,13] Cardiac fibrosis has been demonstrated in PPCM animal models, but has not yet been explored in patients.[4]

PPCM is a disease which progresses quickly to cardiac dysfunction and failure. Its diagnosis is based on exclusion and still remains difficult. PPCM patients present with frequent symptoms of pregnancy, such as dyspnea, fatigue and exercise incapacity which may obscure early signs of heart failure.[14]

One important sign in PPCM is an elevated heart rate (HR). The maternal HR is elevated in normal pregnancy to efficiently eliminate metabolic waste and to cope with the oxygen demand of both the mother and the rapidly developing foetus, but recovers 1 - 2 months after delivery.[15,16] Interestingly, this is not the case with PPCM patients as they continue to display an elevated HR 6 months after delivery which represents 6 times the duration of normal recovery (Figure 1).

Data collected from 27 patients with PPCM at Groote Schuur hospital showed a mean heart rate of 101 ± 3 beats per minute (BPM) at baseline and 83 ± 2 BPM at 6 months (these data confirm a previous publication by Libhaber, et al.[17]). Few patients recover to a healthy heart rate of 75 BPM after 6 months on current standard therapy (see Figure 2). Only 4 patients had recovered to below 75 BPM, this value corresponding with the upper limit of a healthy HR, as per the ESC guidelines.[18]

An elevated HR, at baseline, might be associated with poor outcomes in these patients (Table I). This is in accordance with our recent collaborative study which demonstrates that PPCM patients with elevated HR and low systolic blood pressure had the highest mortality.[17]

Management of acute heart failure in PPCM follows the same principles as those applying to acute heart failure arising from any other cause.[1,18] The drugs most commonly used include diuretics, angiotensin-converting enzyme inhibitors (ACEi) and beta-blockers.

The impact of diuretics on heart failure is mainly symptomatic, via reduced pre-load. ACEi treatment leads to better oxygenation of tissues, lowers blood pressure, and reduces water retention, improving breathing ability and contractility of the heart as secondary outcomes. Beta blockers competitively inhibit the beta adrenergic receptors, improving existing contractility and HR independently of the activation of the sympathetic nervous system. These current treatment strategies have shown to be effective in improving the symptoms of fluid overload and cardiac function. However, our recent observations demonstrated their insufficiency to improve HR in PPCM patients after 6 months of treatment (Figure 2), supporting the idea that targeting HR directly in PPCM may be beneficial.

Experimental studies suggest that reducing HR with an inhibitor of the sino-atrial node, a cluster of cells which serves as the pacemaker of the heart, may be of benefit in the recovery of heart failure.[19]

One such drug which fulfils this purpose is ivabradine, a selective inhibitor of the hyperpolarisation activated cyclic-nucleotide-gated funny current (If) which regulates the pacemaker activity of the sino-atrial node. As such, ivabradine results in HR reduction and targeting HR directly in PPCM may be beneficial. It has been investigated in the SHIFT trial for the treatment of chronic heart failure where it was shown to improve critical outcomes as a complement to other recommended therapy simply by its action on heart rate.[19] In accordance to ESC guidelines, the use of ivabradine may be of interest in PPCM patients as a complementary therapy with an evidence-based dose of beta-blocker (or maximum tolerated dose). Ivabradine may also be used as an alternative to β-blocker in patients with low blood pressure who are intolerant to β-blockers, as it has no ionotropic effects and thus does not alter the strength of contraction of the heart muscle as β-blockers would.[1,18]

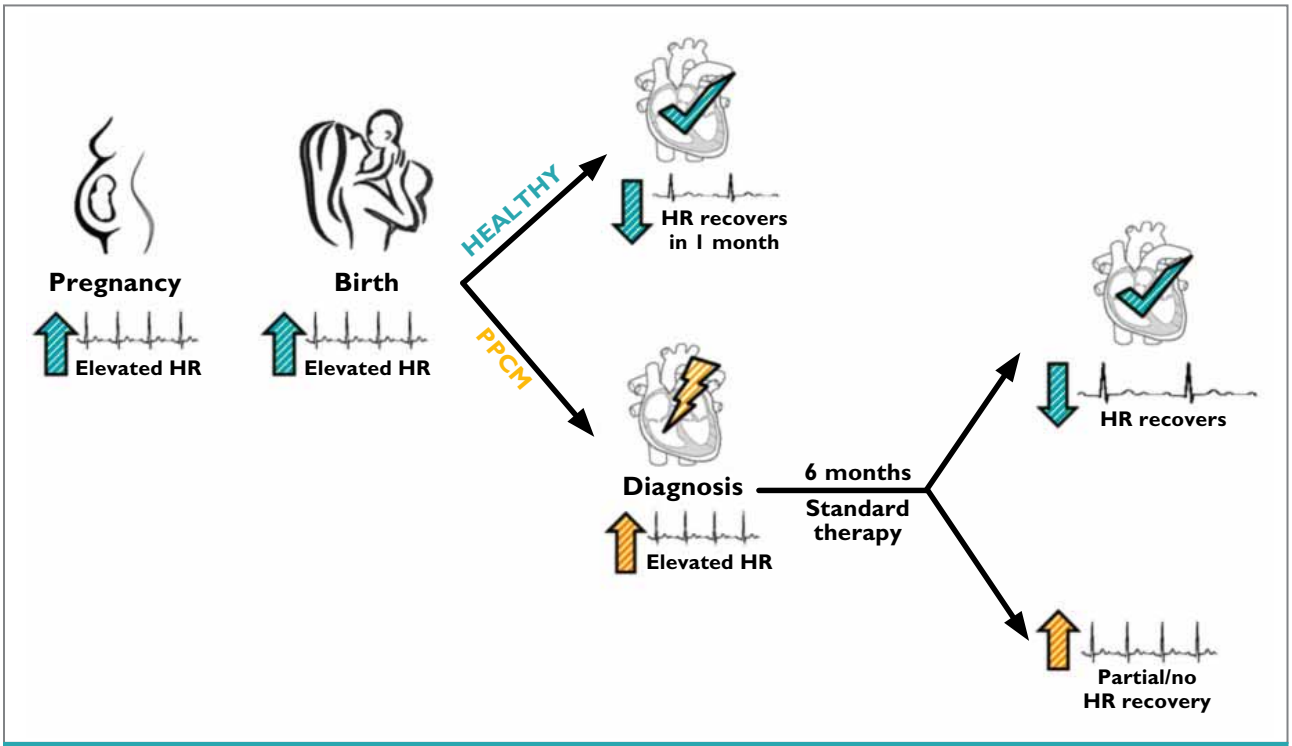

FIGURE 1: Modification of heart rate during pregnancy both in physiological and pathological conditions.

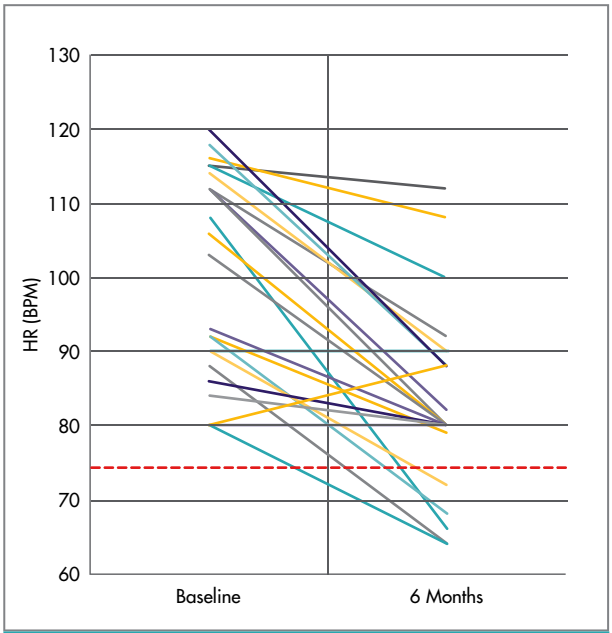

FIGURE 2: Change in heart rate of individual PPCM patients after 6 months on current, recommended therapy. A normal resting HR should be <75 BPM (indicated by the red, dotted line). After 6 months of therapy, only 4 of the 27 patients recover their HR (personal unpublished data).

TABLE I: Cardiac parameters observed in PPCM patients at baseline and after 6 months of current recommended therapy indicates that patients are initially in heart failure (indicated by the left ventricular ejection fraction (EF) <45%), and show some improvement with time. There is also a shift from higher to lower New York heart Association (NYHA) class at baseline compared to 6 months, which reflects this improvement (personal unpublished data).

		Baseline	6 months PP
NYHA class I	n	0	11
	Mean HR (BPM)	-	77 ± 2
	EF (%)	-	50 ± 2
NYHA class 2	n	11	12
	Mean HR (BPM)	97 ± 4	84 ± 4
	EF (%)	33 ± 2	37 ± 3
NYHA class 3	n	14	2
	Mean HR (BPM)	104 ± 4	106 ± 6
	EF (%)	29 ± 3	36 ± 4
NYHA class 4	n	4	0
	Mean HR (BPM)	107 ± 8	-
	EF (%)	23 ± 7	-

Recently HR has been investigated retrospectively as a target to improve the overall outcome in acute heart failure in PPCM patients.[20] Patients with acute PPCM were randomly treated with ivabradine early after diagnosis to evaluate the validity of the hypothesis that the sino-atrial node may be a viable target to improve the outcome of heart failure by means of improving the HR. All patients received guideline-recommended heart failure treatment, including maximally achievable beta-blockade. Despite the small sample size, a significant HR reduction was observed (108 ± 14 BPM at baseline vs. 61 ± 10 BPM at 6-months follow-up visit, $p<0.0001$) and this decease correlated with an improvement of cardiac function (25 ± 9% at baseline vs. 45 ± 8% at 6 months follow-up visit, $p<0.0001$). This preliminary study is a step forward towards improving the management and the outcome of PPCM patients and it further encourages investigations on targeting HR as a potential treatment for these patients.

In addition to its activity on heart rate via the sino-atrial node, ivabradine appears to have secondary effects on cardiac and related systems. In a rodent model, ivabradine reduced ventricular expression of angiotensin-converting enzyme and angiotensin II type 1 receptor (AT1) when used in a model of chronic heart failure following a severe ischaemic event.[21,22] It prevented worsening of left ventricular dysfunction, and improved systemic level endothelial function – perhaps as an indirect effect to HR reduction.[23] Long-term treatment with ivabradine appeared to prevent the deposition of cardiac collagen involved in fibrotic remodeling. These changes in remodeling were associated with cardiac downregulation of the renin-angiotensin-aldosterone system transcripts and occur simultaneously with potent anti-oxidant effects regulated by the reduction of vascular NADPH oxidase activity.[24] It improved endothelial function and modulated the migration of immune cells – lymphocytes in particular, which play a key role in inflammation – this may be the path by which ivabradine attenuates cardiac remodeling.[25]

In conclusion, evidence from both experimental and clinical studies suggests that modulation of the sino-atrial node with drugs such as ivabradine may benefit patients suffering from PPCM. The activity of ivabradine is likely two-fold – direct with regards to heart rate and indirect with long-term structural changes affecting the heart itself, as well as the vascular and endogenous physiological systems. Large clinical trials are needed to validate this concept and further exploration of this hypothesis in an established rodent model of PPCM is required to investigate the outcome on both HR and its effects on other observable systems affected by PPCM.

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