Non Invasive Cardiac Output Evaluation with CO_2 Rebreathing Method for CRT Patients

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Abstract: *Background*: Cardiac resynchronization therapy with ICD (CRT-D) or pacemaker (CRT-P) is useful to reverse the deleterious effects of ventricular dyssynchronia in heart failure (HF) patients. To determinate the responders patients, hemodynamic parameters are difficult to evaluate during follow-up, due to the invasivity of the procedures. We compare hemodynamic response to CRT with cardiac output, not invasively detected (CO2 rebreathing method, Innocor system), with conventional clinical, functional and echocardiographic parameters.

Methods: We enrolled 29 patients affected by end-stage dilated cardiomyopathy treated with CRT-P/CRT-D according to the latest guidelines (NYHA class II-IV, left ventricular ejection fraction [LVEF] ≤ 35%, QRS ≥ 120 ms, sinus rhythm, optimal medical therapy). Patients were evaluated before and after CRT (3 months), considering: NYHA class, Quality of Life score (Minnesota Living with Heart Failure questionnaire), QRS width, echocardiographic parameters (diastolic and systolic left ventricular volumes and related LVEF), six minutes walking test (6MWT) and cardiac output (detected with Innocor system).

Results: Our data showed a significant improvement in Innocor cardiac output 3 months after CRT implant compared to baseline (4.01±0.72 vs 4.48±0.59 l/min, p=0.001). The percentage improvement in cardiac output correlates with the percentage increase in LVEF (25±6% vs 30±7%; r=0.541). The correlation is not statistically significant with NYHA class (from 2.52±0.73 to 1.78±0.60; r=0.098), QoL (from 22.57±15.37 to 9.91±9.14 score; r=0.231) and exercise tolerance (from 390±50 to 437±54 meters; r=0.144).

Conclusions: The Innocor system is a promising non-invasive method to assess the cardiac output at baseline and during follow up in HF patients treated with CRT.

Keywords: Cardiac resynchronization therapy, cardiac output, CO2 rebreathing.

INTRODUCTION

The clinical effects of short and long term cardiac resynchronization therapy (CRT) have been evaluated in a large number of trials with crossover or parallel treatment assignment, using pacemakers (CRT-P) or implantable cardioverter defibrillators (CRT-D) [1-7]. CRT was effective in significant reducing heart failure symptoms and increasing the exercise tolerance. COMPANION [6] and CARE-HF [7] were randomized multi-centre trials showing CRT has been effective on combined primary endpoints of morbidity and mortality. MADIT-CRT [8] and REVERSE [9] trials demonstrated a positive effect of CRT of left ventricular reverse remodelling, reducing heart failure morbidity.

Even if CRT is a recognised treatment modality for patients with dilated cardiomyopathy (ischemic or non ischemic), left bundle branch block, and severe cardiac failure, 30% of treated patients are non-responders. At present, no echocardiographic or clinical parameters could be predictive to discriminate CRT responder patients from non responder ones [10]. When assessed the function of the cardiovascular system, cardiac output (CO) is a substantial parameter: an early positive response with increasing of CO after CRT could be predictive of responder evolution. But hemodynamic parameters are difficult to evaluate during follow-up, due to the invasivity of the procedures. In addition to being accurate, precise, safe and easy to perform, a new method should be non-invasive.

Therefore, cardiac magnetic resonance imaging (CMRI) has become the new non-invasive gold standard for the assessment of cardiac function, nevertheless the technique is expensive, time consuming and not commonly vialable [11]. Inert gas rebreathing (IGR) showed promising results when being compared to the new non-invasive gold standard; however, until recently, the method depended on the use of a medical mass spectrometer, which is expensive and quite complicated to operate and maintain [12]. Recently, a new product, Innocor (Innovision A/S, Odense, Denmark), was introduced using foreign gas rebreathing to measure cardiac output. This product is based on a newly developed insert rebreathing gas analyzer, which is significantly less expensive than a mass spectrometer and much less complex to apply in a clinical environment [13].

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The present study compares the hemodynamic response to CRT with cardiac output, not invasively detected (CO2 rebreathing, Innocor), with conventional clinical, functional and echocardiographic parameters.

PATIENTS AND METHODS

Population

We enrolled 29 patients (22 men, 76%; 7 women, 24%; mean age 72 ± 7.4 years) affected by end-stage dilated cardiomyopathy and treated with CRT-D/CRT-P (22 CRT-D, 76%; 7 CRT-P, 24%) according to the latest guidelines (NYHA class II-IV, left ventricular ejection fraction [LVEF] ≤ 35%, QRS ≥ 120 ms, sinus rhythm, optimal heart failure medical therapy).

The clinical characteristics of the patients are listed in Tables **1** and **2**.

Table 1: Study Enrolled Population

Population	
Patients (n)	29
Male (%)	22 (76%)
Age (years)	72 ± 7.4
DCMP:	
- ischemic	14 (48.3%)
- idiopathic	12 (41.4%)
- valvular	2 (6.9%)
- esotoxic	1 (3.4%)
LVEF (%)	24.89 ± 6.31
QRS (msec)	163.36 ± 25.23
NYHA class	2.54 ± 0.75

Legend: DCMP: dilated cardiomyopathy; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

Six Minutes Walking test could not be performed in 8 patients because of comorbility or non cardiologic disease.

Study Protocol

Patients were evaluated before CRT device implant and after 3 months, considering the following parameters:

- NYHA functional class;
- Quality of Life (Living with Heart Failure Minnesota questionnaire) (14);
- QRS width at a standard ECG (msec);
- Echocardiographic bidimensional parameters: Left Ventricular End Diastolic (LVED) and End Systolic (LVES) volumes (ml); Left Ventricular Ejection Fraction (LVEF),
- Six Minutes Walking Test (6MWT) (meters);
- Cardiac Output (l/min) at rest (detected by Foreign Gas Rebreathing Tecnique: Innocor, Innovision A/S, Odense, Denmark).

Foreign Gas Rebreathing Technique

For the inert gas rebreathing method, we used nitrous oxide (N_2O) blood soluble gas, and sulphur hexafluoride (SF_6) blood insoluble gas, enriched with O_2 concentrations of 0.5% and 0.1% respectively. Tidal volume was progressively increased in the closed circuit to match the physiologic increase. Use of SF_6 allowed to measure the volume of lungs, valve and rebreathing bag. N_2O concentration decreases during the rebreathing maneuver, with a rate proportional to pulmonary blood flow (PBF) [15].

Gas was sampled continuously from the mouthpiece for analysis by the inert gas rebreathing analyser of Innocor. A constant ventilation rate was ensured by having the subject breath in synchrony with a graphical tachometer on the computer screen, and a constant ventilation volume was ensured by requesting the subject to empty the rebreathing bag completely with each breath.

The rebreathing system software calculated Stroke Volume (SV) from the rate of uptake of N_2O into the blood (slope of the regression line through logarithmically transformed expiratory N_2O concentration plotted against time). After correction for system volume changes using SF_6 concentration the first two or three breaths were excluded from the analysis due to initial incomplete gas mixing [16]. According to the recommendations of Damgaard [12], the rebreathing maneuver was started after a normal expiration at a breathing rate of 20/min.

The operating principle of Innocor is to let the patient breathes minute quantities of a blood soluble and an insoluble gas in a closed breathing assembly for a short period. The blood flowing through the lungs (effective pulmonary blood flow, PBF) absorbs the blood soluble gas and therefore the disappearance rate is proportional to the blood flow. Other factors affecting the distribution of the blood soluble gas are accounted for by also measuring the blood insoluble gas.

Table 2: Basal Parameters of Enrolled Patients

No	Age (years)	DCMP (etiology)	QRS (msec)	NYHA class	QoL (score)	6MWT (meters)	LVEF (%)	EDV (ml)	ESV (ml)	CO (l/min)
1	76	idiopathic	178	2	19		19	220	178	3.3
2	76	idiopathic	178	2	9		13	152	132	5.2
3	73	ischemic	148	2	10		30	172	120	4.0
4	84	ischemic	160	3	48		25	118	89	3.3
5	78	idiopathic	176	4	45	380	17	180	150	2.2
6	75	idiopathic	168	2	8	400	31	125	86	3.9
7	73	ischemic	144	2	11	385	34	177	116	5.3
8	71	idiopathic	160	2	15	360	24	210	160	4.2
9	69	ischemic	140	2	21	360	30	141	99	4.2
10	81	idiopathic	130	4	35	280	32	122	83	3.1
11	73	ischemic	160	2	10	370	21	135	107	3.9
12	76	ischemic	200	2	14	390	15	336	284	3.8
13	66	ischemic	136	3	16	480	31	193	134	3.8
14	61	esotoxic	160	2	10	380	21	322	267	6.5
15	68	idiopathic	160	3	21		25	169	122	3.7
16	55	ischemic	128	2	50	480	21	205	154	4.5
17	76	ischemic	160	2	1	370	22	262	205	4.5
18	72	ischemic	124	3	22		25	209	156	3.4
19	54	idiopathic	120	3	33	350	13	178	154	3.8
20	73	ischemic	178	3	33	420	23	288	221	4.3
21	77	idiopathic	190	2	15	300	17	128	106	3.9
22	83	idiopathic	160	2	5	450	34	118	78	2.7
23	70	idiopathic	200	4	50		24	205	155	3.2
24	71	idiopathic	170	2	12	360	29	224	160	4.9
25	64	valvular	168	3	6	350	28	172	123	4.7
26	75	idiopathic	120	2	15	400	28	150	108	3.9
27	76	valvular	222	2	21	480	33	168	112	5.5
28	69	ischemic	160	3	17	480	30	264	186	3.3
29	84	idiopathic	200	4	45		27	106	77	3.3

Legend: DCMP: dilated cardiomyopathy; NYHA: New York Heart Association; QoL: quality of life; 6MWT: six minutes walking test, LVEF: left ventricular ejection fraction, EDV: left ventricular end-diastolic volume; ESV: left ventricular end-systolic volume; CO: cardiac output (Innocor system).

The spontaneously breathing patient puts on a nose clip and breathes into a respiratory valve via a mouthpiece and bacterial filter. At the end of expiration the valve is activated so that the patient will breathe in and out (rebreathe) from a rubber bag for a period of 10-20 seconds. The patient is asked to empty the bag during each inspiration and breathe with a slightly increased respiration rate. After this period the patient is switched back to ambient air and the test is terminated. The bag is prefilled with an oxygen (O_2) enriched mixture containing two foreign gases; typically 0.5% nitrous oxide (N_2O) and 0.1% sulphur hexafluoride (SF_6). These gases and CO_2 are measured continuously and simultaneously at the mouthpiece by a photoacoustic gas analyser inside Innocor (Figure **1**).

N_2O is soluble in blood and is therefore absorbed during the blood's passage of the lungs at a rate, which is proportional to the blood flow. So, the higher the cardiac output the higher the disappearance rate (slope of measured gas curve). SF_6 is insoluble in blood and

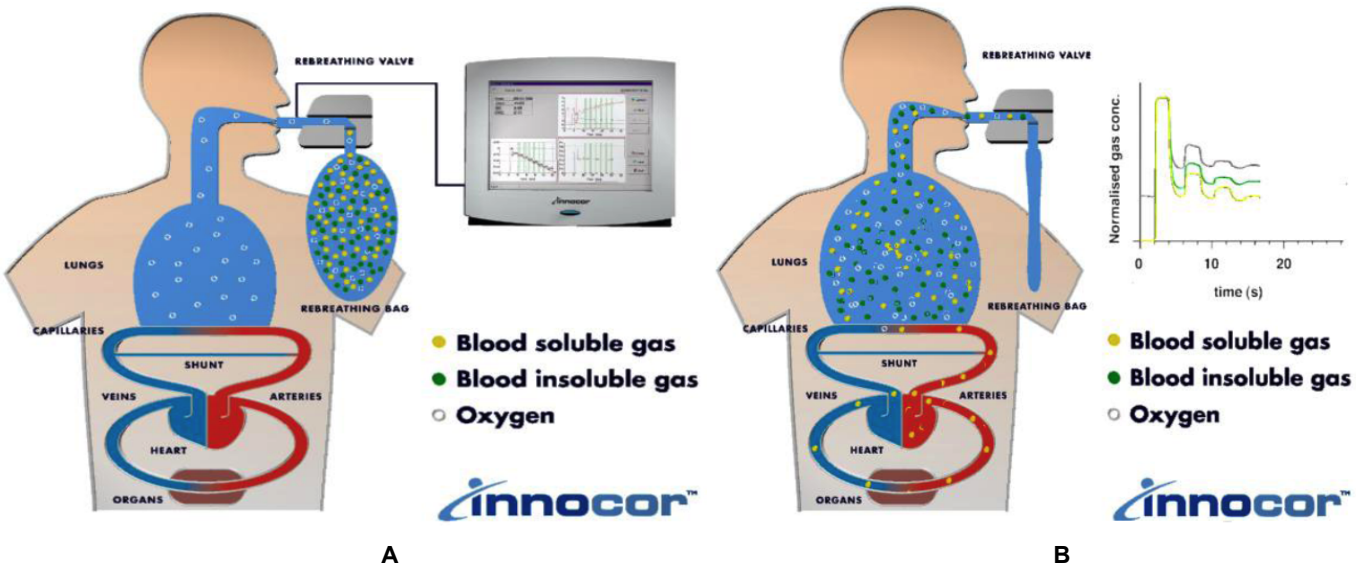

Figure 1: Cardiac Output evaluation with gas distribution trends during rebreathing.
Soluble, insoluble and oxygen gas within the rebreathing bag (**A**) and after rebreathing patient lungs (**B**); see text for details.

therefore stays in the gas phase and is used to determine the lung volume from which the soluble gas is removed.

The rebreathing test can be performed as a single test at rest or at a given exercise level using a bicycle ergometer or a treadmill in a stand-alone configuration. Alternatively it can be performed as a part of an exercise protocol where rebreathing maneuvers are done at pre-programmed intervals/workloads. By using a pulse oximeter, the heart rate (HR) can be measured during the test and used to derive the Cardiac Output (CO). The arterial oxygen saturation (SpO_2) indicates whether the oxygenation is normal and thus if there is a significant intrapulmonary shunt (SpO_2 < 95%) [12].

Statistic Analysis

Data are expressed as the mean and Standard Deviation (SD). We compared data using T Student test and a p value of <0.05 was considered statistically significant.

We correlated data using Pearson regression analysis.

Pearson's correlation coefficient between two variables is defined as the covariance of the two variables divided by the product of their standard deviations:

$$r_{xy} = \frac{\sigma_{xy}}{\sigma_x \sigma_y}$$

where

- σ_{xy} is covariance between X and Y;

- σ_x and σ_y are standard deviations.

The correlation coefficient ranges from −1 to 1: $1 < r_{xy} < 1$. A value of 1 implies that a linear equation describes the relationship between X and Y perfectly, with all data points lying on a line for which Y increases as X increases. A value of −1 implies that all data points lie on a line for which Y decreases as X increases. A value of 0 implies that there is no linear correlation between the variables.

Correlation can be defined:

$0 < r_{xy} < 0.3$ → weak;

$0.3 < r_{xy} < 0.7$ → moderate;

$r_{xy} > 0.7$ → strong.

RESULTS

All patients were evaluated before and 3 months after CRT. Five patients were excluded for insufficient compliance during gas rebreathing test (17% reliability of the rebreathing technique); one patient was excluded from the study because of atrial fibrillation onset before the 3 month control.

Clinical and instrumental parameters, evaluated using t Student analysis, had a significant improvement (Table **3**).

Table 3: Clinical and instrumental parameters (mean ± standard deviation) at baseline and 3 months after CRT (23 patients evaluated after 5 patients exclusion for insufficient compliance during gas rebreathing test); p value for statistic analysis using t Student test for paired data

Parameters	Baseline (before CRT)	Follow up (3 months after CRT)	P value
QRS (msec)	164,61 ± 26,79	140, 70 ± 21,03	0,00178
NYHA class	2,52 ± 0,73	1,78 ± 0,60	$5,27 \times 10^{-5}$
QoL (score)	22,57 ± 15,37	9,91 ± 9,14	$1,49 \times 10^{-5}$
6MWT (m)	390,30 ± 50,20	437,06 ± 53,59	0,00232
EDV (ml)	185,30 ± 55,53	172 ± 47,85	0,04212
ESV (ml)	140 ± 48,30	121,61 ± 40,05	0,00470
EF (%)	24,65 ± 5,87	30,09 ± 6,95	0,00012
CO (l/min)	4,01 ± 0,72	4,48 ± 0,59	0,0013

Legend: see Table **2**.

Our data showed a significant improvement in LVEF and Innocor Cardiac Output 3 months after CRT implant compared to baseline: LVEF: 25 ± 6% baseline versus 30 ± 7% after CRT, p = 0.00012 (Figure **2**); CO: 4.01 ± 0.72 l/min baseline versus 4.48 ± 0.59 l/min after CRT, p = 0.0013 (Figure **3**). The increase in cardiac output was on average 13%.

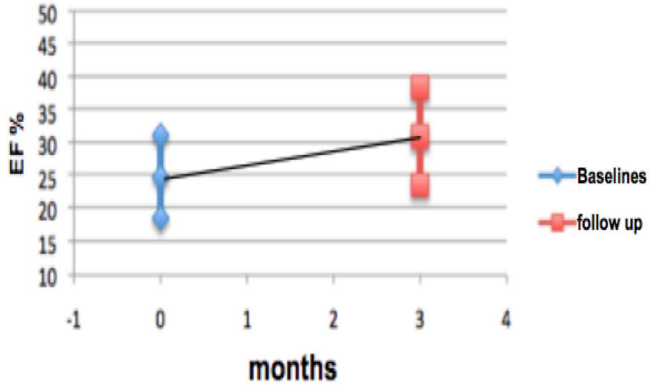

Figure 2: Left Ventricular Ejection Fraction (mean and standard deviation) at baselines (24.89 ± 6.31 %) and after 3 months of CRT follow up (31.04 ± 7.41 %).

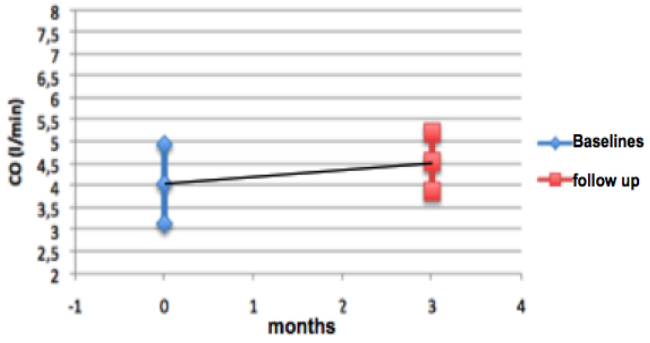

Figure 3: Innocor detected Cardiac Output CO (mean and standard deviation) at baselines (4.04 ± 0.9 l/min) and after 3 months of CRT follow up (4.55 ± 0.67 l/min).

The percentage improvement in cardiac output determined with Innocor has been correlated with the percentage increase of the other parameters.

The percentage improvement in cardiac output determined with Innocor correlates with the percentage increase in left ventricular ejection fraction (r = 0.541) (Figure **4**). The correlation is not statistically significant with NYHA class (r = 0.098), QoL (r = 0.231) and exercise tolerance (r = 0.144).

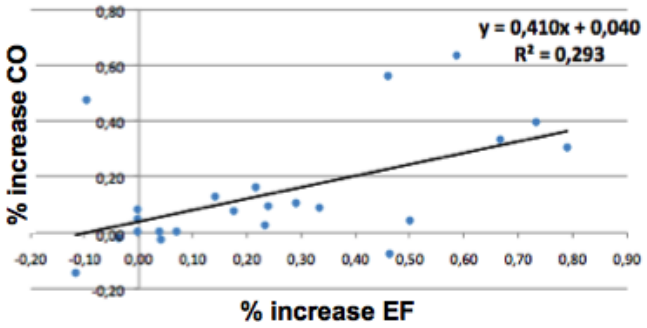

Figure 4: The percentage improvement in cardiac output determined by Innocor correlates with the percentage increase in EF detected by echocardiography.

The study population was evaluated two years after CRT device implant with retesting of NYHA functional class and left ventricular ejection fraction; 2 patient died for non-cardiovascular complications. In the others patients we observed a stable improvement of NYHA class (1.18±0.50 versus 1.79±0.63) and LVEF (36.2±8.9 versus 31.04±7.41); these data confirmed that our patients were “responders” to CRT.

DISCUSSION

Large randomized controlled trials (RCTs) have demonstrated the benefit of CRT (with or without

defibrillation) in patients with left ventricular dysfunction (EF <35%), ventricular desynchronization and reduced NYHA functional class, in optimized therapy [1-7]. All RCTs have confirmed a significant alleviation of symptoms and increase in exercise capacity conferred by CRT.

The clinical response of patients after CRT implant can be very variable. On average, NYHA function class decreased by 0.5–0.8 points, the 6 min walk distance increased by 20%, and peak oxygen consumption increased by 10–15%. The functional benefits and quality of life improvements were sustained.

A consistent finding in the randomized trials designed with up to 6 months of follow-up has been an up to 15% absolute reduction in LV end-diastolic diameter and an up to 6% increase in LVEF following CRT [8, 9]. A baseline typical left bundle branch block (LBBB) pattern predicted a favourable outcome.

Instead of this benefit, CRT non-responder rates of 25% to 30% have been reported in clinical studies. Hemodynamics parameters are not considered in determination of CRT effects because of cost and risk of catheterization. Measurements of cardiac output by standard methods, such as the direct Fick method or the thermodilution method, are time consuming and require cardiac catheterization, which is associated with a potential risk of adverse events. Therefore these methods are not feasible for routine patient monitoring in larger population groups.

Foreign gas rebreathing with continuous analysis of ventilatory gas concentrations is an easy, safe and well established method for non-invasive measurements of effective pulmonary blood flow (QEP), which is equivalent to cardiac output in the absence of intrapulmonary shunt flow. In the past, measurements of QEP and of cardiac output by foreign gas rebreathing have been performed using mass spectrometers. Mass spectrometers, however, are bulky, difficult to operate, and require frequent calibration and maintenance [12]. These factors have significantly limited the clinical application of measurements of cardiac output by gas rebrathing. More recently, an accurate infrared photoacoustic gas analyser has been introduced for the continuous analysis of ventilatory gas concentrations [16]. Compared with conventional mass spectrometers, this analyser weighs less, and is less expensive, more user friendly and stable, which markedly facilitates clinical use [15].

Saur *et al*. [17] have documented the reliability of Innocor, comparing this technique with cardiac MRI, considered the gold standard among non-invasive methods. They have shown that there is a good correlation between the parameters obtained by the method of gas rebreathing in the closed circuit and cardiac magnetic resonance imaging (CMRI). The precision of the measurements performed at rest was significantly better in the physiological range, but technique seems to be less reliable for values that deviate much from the normal range. Even in our study, according with literature [16], 17% of population (5 patients) was unable to perform gas rebreathing test for insufficient compliance at basal or at the control test.

In our experience, the measurement of cardiac output at rest with Innocor has proven useful to better define "responders" to CRT.

The primary focus of the present study was to compare clinical and instrumental parameters at the baseline and 3 months after CRT implant to confirm a significant improvement. We demonstrated a significant improvement of all parameters: NYHA class (2.54±0.75 vs 1.79±0.63); QoL (21.25±14.89 vs 10.04±9.72 scores); exercise tolerance (391.67±56.64 vs 439.05±66.85 meters at 6MWT); left ventricular ejection fraction (24.89±6.31 vs 31.04±7.41); cardiac output measured by foreign gas rebreathing technique (4.04±0.9 vs 4.55±0.67 l/min).

The second focus of this study was to compare the percentage improvement in cardiac output determined with Innocor with the percentage increase in clinical and instrumental parameters. The correlation was statistically significant with ventricular ejection fraction (r = 0.541), but it was not statistically significant with NYHA class (r = 0.098), QoL (r = 0.231) and exercise tolerance (r = 0.144).

Although, the direct Fick method is the gold standard of cardiac output measurement, it is rarely accepted by clinical doctors or patients because of its risk and complexity. Inerte gas rebreathing cardiac output measurements showed only a small bias and a good reproducibility when compared to invasive [15, 16, 18, 19, 20], as well as non-invasive reference techniques [17].

CONCLUSION

The foreign gas rebreathing technique is an easy, safe and well established method for non-invasive

measurement of cardiac output with good prospects for clinical application in heart disease patients. The Innocor system is also a promising non-invasive method to assess the cardiac output at baseline in HF patients with CRT; maybe in the future it could be assessed also during a submaximal exercise test.

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