

SHORT COMMUNICATION

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# Validation of Non-invasive Measurement of Cardiac Output: Using Whole-Body Bio-impedance Versus Inert Gas Rebreathing in Healthy Women Undergoing In Vitro Fertilisation

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## Abstract

**Background:** Haemodynamic assessment in and before pregnancy is becoming increasingly important in relation to pregnancy complications and outcomes. Different methodologies exist but there is no gold-standard technique for non-invasive measurement of cardiac output (CO). We sought to assess two methods of CO measurement in healthy women undergoing in vitro fertilisation cycles (IVF). This was a prospective longitudinal study of 71 women aged 18–44 years planning IVF undergoing CO measurements obtained via inert gas rebreathing (IGR) using Innocor™ and whole-body bio-impedance (WBI) using Nicas™ to assess the reproducibility between the methods. Four visits occurred at which both techniques were used: initial assessment, embryo transfer, day of pregnancy test and 4 weeks post-transfer (regardless of whether conception occurred). Cross-sectional agreement of the methods was assessed using the calculation of bias, percentage error and limits of agreement (LOA) via the Bland–Altman analysis. Longitudinal agreement of the methods was assessed using a 4-quadrant plot with concordance rate, angular bias and radial limits of agreement (%).

**Results:** One hundred and thirteen measurements from 44 participants were suitable for cross-sectional (Bland–Altman) analysis. IGR (Innocor™) Mean CO was 4.61 L/min and 5.05 L/min with WBI (Nicas™). The bias was 0.44 L/min. The percentage error was 76% and intra-correlation coefficient was 0.135 (95% CI –0.43–0.306). Fifty-nine measurements from 28 participants were suitable for longitudinal (4Q-plot) analysis. The concordance rate was 64.4%, angular bias –0.14, and radial limits of agreement + – 13.25°.

**Conclusion:** There was poor cross-sectional and longitudinal agreement between inert gas rebreathing and whole-body bio-impedance techniques. These techniques cannot be used interchangeably when measuring CO in women undergoing IVF, and these results may be more generalizable, to women in the peri-conception period.

**Keywords:** Cardiovascular, Maternal haemodynamics, Non-invasive, Assisted reproductive techniques, In vitro fertilisation

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## 1 Background

Disordered cardiovascular adaptation in pregnancy is associated with pre-eclampsia and growth-restricted babies [1]. The known acute effects of IVF on maternal



haemodynamics are limited [2] and no gold-standard method for non-invasively measuring CO in this population exists. In fresh IVF cycles, ovarian stimulation leads to acutely supra-physiological oestradiol [3], not experienced in spontaneous conception. Frozen embryo replacement cycles (FET) require no ovarian stimulation and have no corpus lutea, which has been associated with cardiovascular maladaptation and increased pre-eclampsia risk in FET conceived pregnancies [4, 5].

Invasive methods of measuring CO are unacceptable in healthy women trying to conceive. Innocor™ (Innovision, Denmark) uses inert gas rebreathing (IGR) to calculate CO and compares well to cardiac MRI [6]. Nicas™ (Niccom, Israel), utilises whole-body bio-impedance (WBI) and compares favourably with Doppler echo, with a correlation of (R) 0.81 [7].

**2 Aim**

To compare the whole-body impedance (WBI) Nicas™ method to the inert gas rebreathing Innocor™ method of evaluating cardiac output in women undergoing in vitro fertilisation.

**3 Methods**

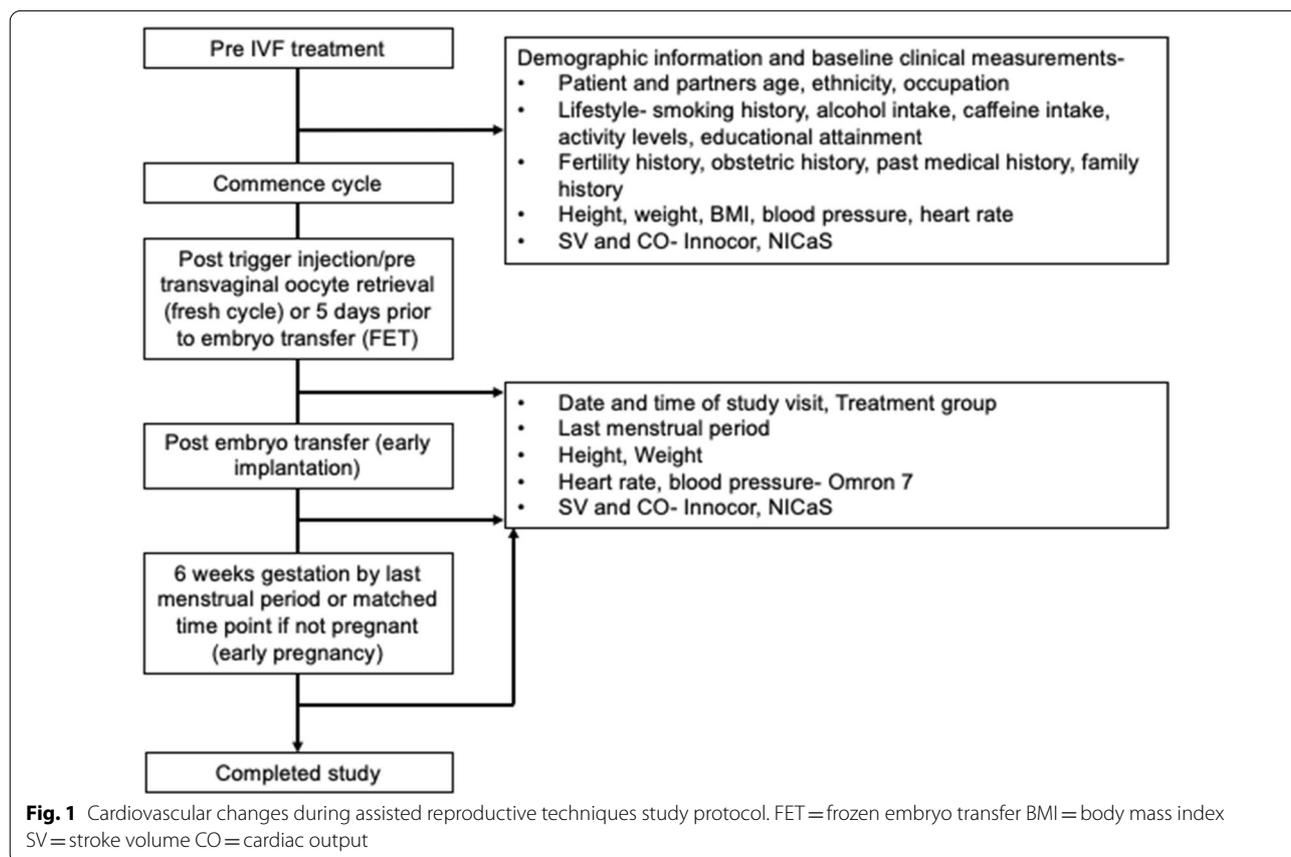
We conducted a prospective longitudinal cohort study, recruiting healthy women aged 18–44 years between 23rd September 2018 and 4th December 2019, planning to undergo IVF. By virtue of UK NHS IVF funding criteria, all had a BMI under 30 and were non-smokers. Women underwent fresh (ovarian stimulation) cycles and frozen embryo replacement cycles (FET). The study protocol is summarised in Fig. 1.

Women were recruited via one inner city fertility clinic and gave written consent. Exclusion criteria were: pre-existing chronic medical co-morbidity, including cardiovascular disease.

Four study visits occurred (Fig. 1), prior and post-embryo transfer.

At each visit, cardiac output was assessed non-invasively via inert gas rebreathing (IGR) using the Innocor™, and whole-body bio-impedance (WBI) using the Nicas™, consecutively in that order. IGR was taken as the reference technique as the more established method which has compared favourably with invasive methods and cardiac magnetic resonance imaging (MRI) [6, 8].

The process and sequence of measurements were the same for every study visit and patients were refrained



from caffeinated drinks and strenuous exercise for at least two hours prior to the visit. Patients were acclimatised in a temperature-controlled room for 10 min prior to measurements being recorded.

Data were analysed using IBM SPSS Version 24.0

#### 4 Cross-sectional Analysis

Absolute values of simultaneous CO measurements with both techniques obtained at each visit were used for comparison. There was no correction for repeated measurements within subjects between visits. Agreement was assessed using Bland–Altman (BA) plots and statistics and intraclass correlation. BA statistics included mean CO, bias (reflecting accuracy), limits of agreement and percentage error (reflecting precision). Good agreement was considered with a low bias (<0.75 L/min), percentage error < 30% and intra-correlation coefficient (ICC) > 0.75 L/min.

#### 5 Longitudinal Analysis

Trending capacity of both techniques was compared using 4-quadrant plot a concordance analysis. Differences in cardiac output ( $\Delta$ CO) between 2 consecutive visits (1–2, 2–3, 3–4 and 1–4) were compared between both techniques. An exclusion zone of 0.5 L/min was considered. Concordance was calculated along with angular bias and radial limits of agreement. Acceptable agreement was to be defined as a concordance rate > 90% with angular bias < 5° and RAL + – 30° [9].

#### 6 Results

Seventy-one patients were recruited over a 1-year period (September 2018–December 2019). Thirty-four patients underwent frozen cycles (FET) and 39 had fresh cycles. Baseline demographics for all participants are shown in Table 1.

Cross-sectional analysis required paired measurements from both devices at the same time point, therefore, a total of 113 paired measurements taken from 44 participants were suitable for Bland–Altman analysis. A visual representation of the agreement in CO measurements between the two devices was constructed using a Bland–Altman plot; see Fig. 2. Mean CO was 4.61 L/min and 5.05 L/min for Innocor™ and Nicas™, respectively. The bias was 0.44 L/min and the LOA were 3.24 to – 4.12. The percentage error was 76%. The ICC was 0.135 (95% CI – 0.43–0.306).

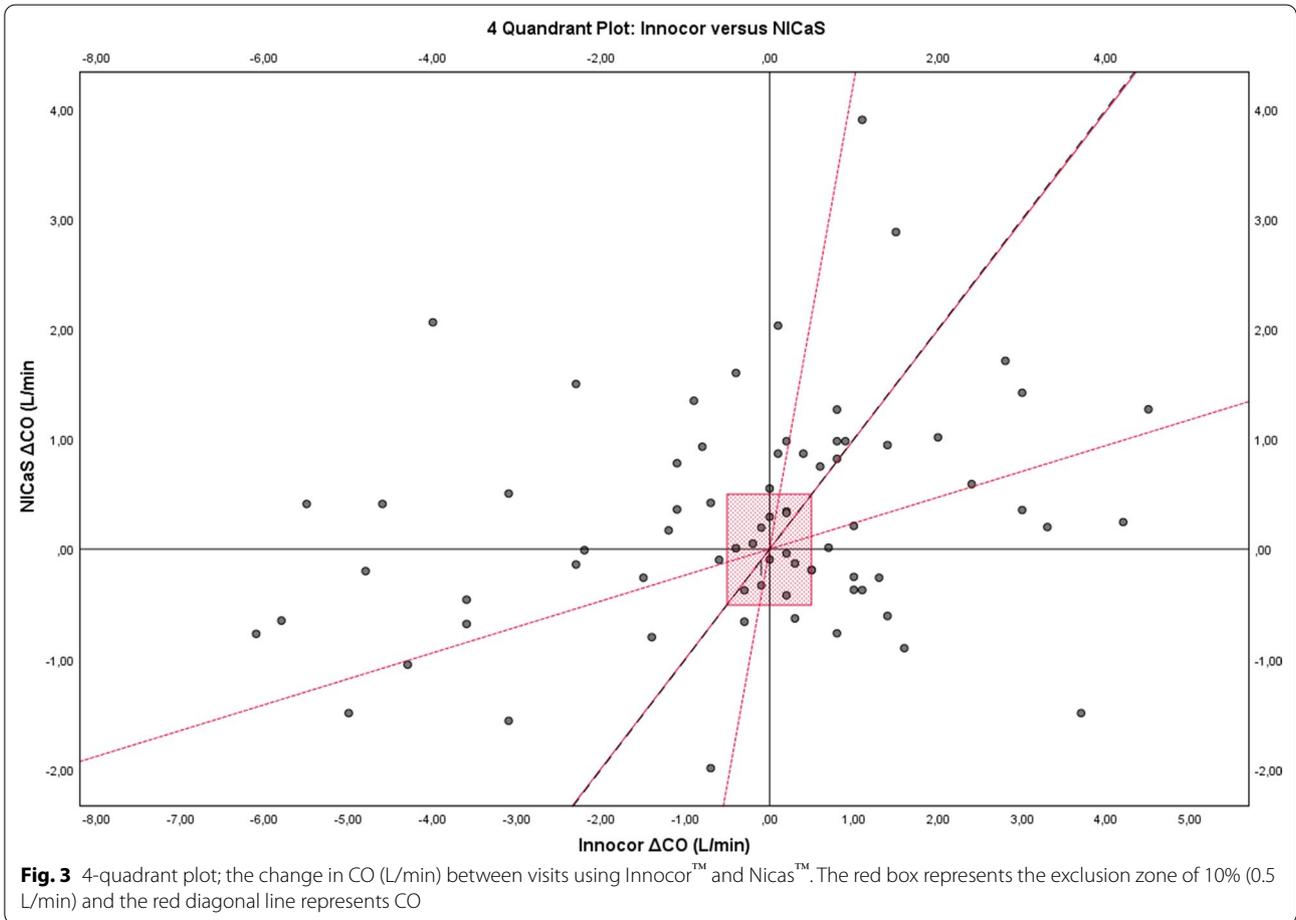
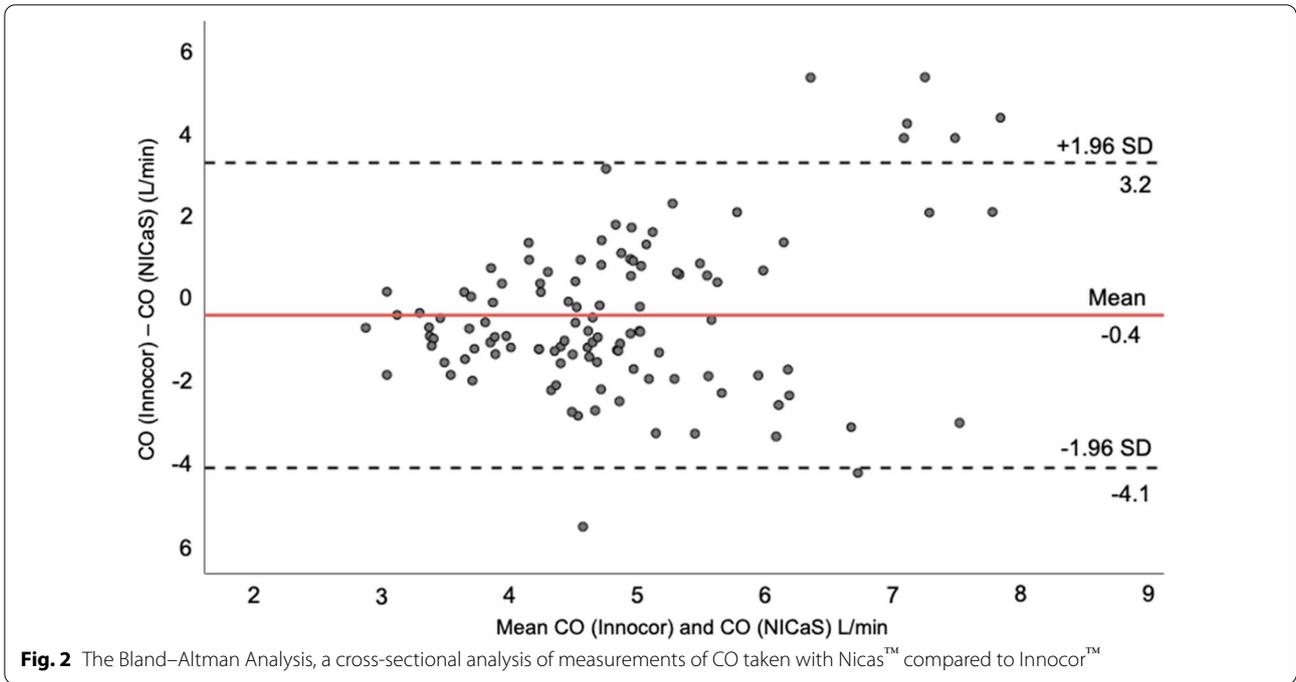
Longitudinal analysis required paired measurements from both devices across incremental visits; therefore, 59 measurements from 28 participants were suitable for the 4-quadrant plot; see Fig. 3.

Concordant results, i.e. where the devices detect a change in CO in the same direction are demonstrated in the upper right and lower left quadrants. Non-concordant results, i.e. where the devices detect a change in CO in opposite directions are represented by data points in the upper left and lower right quadrants. The concordance rate between the devices was 64.4%, angular bias was – 0.14°, and radial limits of agreement + – 13.25%.

**Table 1** Demographic data

	All participants	Participants included in cross-sectional comparison of CO	Participants included in longitudinal comparison of CO
Participants (n)	71	44	28
Mean maternal age—years (SD)	35.03 (4.08)	34.82 (3.75)	35.43 (3.39)
Caucasian, n (%)	34 (47.9)	23 (51.1)	14 (50)
Asian, n (%)	20 (28.2)	11 (24.4)	5 (17.9)
Black, n (%)	7 (9.86)	6 (13.3)	5 (17.9)
Other ethnicity, n (%)	10 (13.2)	5 (11.1)	4 (14.3)
Mean alcohol intake-units (SD)	1.7 (2.63)	1.75 (2.90)	2.04 (3.25)
Mean caffeine intake-cups/day (SD)	1.46 (1.52)	1.51 (1.56)	1.5 (1.64)
Smokers, n (%)	13 (17.1)	9 (20)	6 (21.4)
Mean body mass index (SD)	24.76 (3.66)	24.87 (3.39)	25.12 (3.28)
Mean body surface area-m <sup>2</sup> (SD)	1.72 (0.15)	1.73 (0.16)	1.73 (0.16)

All participants and further specified for those used in the Bland–Altman and longitudinal analysis  
CO cardiac output, SD standard deviation



## 7 Discussion

There is emerging interest in assessing cardiac output and other cardiovascular parameters, cross-sectionally and longitudinally prior and during pregnancy. There is evidence that blood pressure prior to pregnancy is associated with risk of pre-eclampsia [10] and low cardiac output prior to pregnancy in healthy women is associated with the development of pre-eclampsia or growth-restricted babies [11]. In addition to these considerations, the supra-physiological doses of hormonal drugs used in IVF may have a profound effect on the maternal cardiovascular system, albeit for a short time.

In this, the only study of its type, we compared a relatively newer method of WBI to IGR, which has been favourably compared to other methods such as cardiac MRI [6]. A large number of paired readings were used to compare IGR using Innacor™ and WBI using Nicas™ cross-sectionally and longitudinally. Bias (0.44 L/min) was within accepted limits which demonstrates reasonable accuracy but a wide LOA and PE of 76% and low ICC shows limited precision and, therefore, poor agreement between both the methods.

Comparison of trending capacities of both devices showed a concordance rate (76%) far below the generally accepted 90% level for good agreement.

To our knowledge, this is the only study comparing the two techniques, and has a large number of measurements, making the findings robust. In conclusion, it is not possible to use these non-invasive methods interchangeably, for absolute measurements or for trend analysis with time as agreement for both absolute CO measurements and tracking changes in CO between these techniques is limited.

### Abbreviations

BA: Bland–Altman; BMI: Body mass index; CO: Cardiac output; FET: Frozen embryo transfer; ICC: Intra-correlation coefficient; IGR: Inert gas rebreathing; IVF: In vitro fertilisation; LOA: Limits of agreement; SD: Standard deviation; SV: Stroke volume; WBI: Whole-body bio-impedance.

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### Author Contributions

The authors RJ and CL wrote the study protocol and submitted and obtained ethical approval. RJ and MA carried out patient recruitment, data collection and interpretation. DR and JC performed the statistical analysis. RJ and MA wrote the paper with the supervision of CL and input from DR and JC.

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### Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Declarations

### Conflict of Interest

The authors declare that they have no competing interests.

### Ethical Approval

Granted by Cambridge East NEC in August 2018.

### Consent for Publication

Not applicable.

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