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Original Research

Sympathomodulation in Heart Failure with High vs. Normal Ejection Fraction

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ABSTRACT

Background: Despite recent advances in the treatment of heart failure with preserved ejection fraction (HFpEF), the overall outcome is poor and evidence-based therapeutic options are scarce. So far, the only evidence-based therapy in HFpEF, sodium glucose linked transporter 2 inhibitors, has only insignificant effects in patients with a high EF (EF > 60%, HEF) when compared to a normal EF (EF 50%-60%, NEF). This could be explained by different biomechanical and cellular phenotypes of HFpEF across the range of EFs rather than a uniform pathophysiology. We aimed to investigate the concept of different phenotypes in the HEF and NEF using noninvasive single-beat estimations and to observe alterations in pressure-volume relations in both groups following sympathomodulation using renal denervation (RDN).

Methods: Patients from a previous study on RDN in HFpEF were stratified by having HFpEF with an HEF or NEF. Single-beat estimations were used to derive arterial elastance (Ea), end-systolic elastance (Ees), and diastolic capacitance ($VPED_{20}$).

Results: Overall, 63 patients were classified as having an HEF, and 36 patients were classified as having an NEF. Ea did not differ between the groups and was reduced at follow-up in both groups ($p < 0.01$). Ees was higher and $VPED_{20}$ was lower in the HEF than those in the NEF. Both were changed significantly at follow-up in the HEF but not in the NEF. Ees/Ea was lower in the NEF (0.95 ± 0.22 vs 1.15 ± 0.27, $p < 0.01$) and was significantly increased in the NEF (by 0.08 ± 0.20, $p < 0.05$) but not in the HEF.

Conclusions: Beneficial effects of RDN were observed in the NEF and HEF, supporting the further investigation of sympathomodulating treatments for HFpEF in future trials.

ABBREVIATIONS

AAD, ascending aortic distensibility; BP, blood pressure; CMR, cardiac magnetic resonance imaging; E_a, arterial elastance; EDP, end-diastolic pressure; EDPVR, end-diastolic pressure-volume relation; EDV, end-diastolic volume; E_{es}, end-systolic elastance; EF, ejection fraction; ESPVR, end-systolic pressure-volume relation; ESV, end-systolic volume; HEF, high ejection fraction; HFpEF, heart failure with preserved ejection fraction; LV, left ventricle/ventricular; LVEF, left ventricular ejection fraction; NEF, normal ejection fraction; P_{es}, end-systolic pressure; RDN, renal denervation; SV, stroke volume; VAC, ventricular-arterial coupling; $VPED_{20}$, Volume at normalized end-diastolic pressure of 20 mmHg; $VPES_{100}$, Volume at normalized end-systolic pressure of 100 mmHg.

Introduction

Despite the recent progress in the treatment of heart failure with preserved ejection fraction (HFpEF),[1] overall treatment options in these often multimorbid patients are limited.[2] So far, the only evidence-based therapy in HFpEF, sodium glucose linked transporter 2 inhibitors, have only insignificant effects in patients with high ejection fraction (>60%, HEF) when compared with mildly reduced (40%-50%) to normal ejection fraction (50%-60%, NEF). Theoretically, this difference might partly be explained by different phenotypes and pathophysiologic pathways in patients with HFpEF and HEF vs. NEF, as recent work from our group suggests.[3] Although patients with HEF are characterized by a higher resting contractility and an

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impaired contractile reserve, patients with NEF show more fibrosis and a phenotype more similar to the one observed in heart failure with reduced ejection fraction (EF).

Patients with heart failure are often characterized by an elevated sympathetic tone[4] and an impaired ventricular-arterial coupling (VAC).[5] Following this thought and previous results from smaller previous studies,[6,7] a standardized sympathomodulating intervention such as renal denervation (RDN) likely has overall beneficial effects on the interaction between the arterial system and the ventricle in HFpEF but might have different effects in patients with HEF and NEF.

Therefore, we aimed to (1) confirm the observations from our recent study[3] in a different cohort using noninvasive estimation of left ventricular (LV)-filling pressures and single-beat estimation of end-systolic and end-diastolic pressure-volume relations (ESPVR and EDPVR, respectively) and to (2) investigate the effects of a sympathomodulation using RDN in patients with HEF vs. NEF and HFpEF.

Methods

Study Design and Patient Cohort

This study was designed as a retrospective analysis of our previous work. The details on the patient inclusion have been published previously.[7] In brief, patients undergoing RDN for uncontrolled arterial hypertension (on stable medication for at least 4 weeks) were screened for clinical and echocardiographic signs of HFpEF and elevated NT-proBNP. Patients with LVEF ≥50%, elevated NT-proBNP, echocardiographic evidence of structural or functional abnormalities as defined by the European Society of Cardiology 2016 guidelines, and heart failure signs or symptoms (or loop diuretic treatment in their absence) were classified as having HFpEF as reported previously.[2,7] Only patients with HFpEF were included in the current analysis. Patients with more than mild mitral or aortic valve disease were excluded from the analysis.

Echocardiography, ambulatory blood pressure monitoring readings, NT-proBNP levels and, in a subgroup of patients, cardiac magnetic resonance (CMR) imaging were acquired before and within 6 months post-RDN.

Patients were classified as having NEF (50%-60%) or HEF (>60%) according to baseline echocardiography.

Echocardiographic Assessment and Single-Beat Estimations

Standard transthoracic echocardiographic assessment was performed before and after RDN with noninvasive arm cuff blood pressure (BP) measurements. Central BP was assessed in a subgroup using the Complior device (Complior Analyse, 2011, ALAM Medical, Saint Quentin Fallavier, France) and estimated as previously described in the remaining patients.[7] LV ESPVRs and EDPVRs were estimated noninvasively using single-beat methods as described previously by Chen et al. and Klotz et al., respectively.[8,9] End-systolic elastance (E_{es}) was defined as the slope of ESPVR and volume-axis intercept (V_0) was the intersection of the ESPVR with the volume axis. E_a was defined as the ratio between end-systolic pressure (P_{es}) and stroke volume (SV). End-diastolic pressure (EDP) was calculated from the formula $EDP = 11.96 + E/E' \times 0.596$.[10] To simplify comparisons of ESPVRs and EDPVRs between groups, the volumes for a given end-systolic pressure of 100 mm Hg ($VPES_{100}$) and for a given EDP of 20 mm Hg ($VPED_{20}$, diastolic capacitance) were calculated (Figure 1). VAC was indexed by E_{es}/E_a.

CMR Imaging

CMR scans were performed by a standardized protocol to assess aortic flow and ascending aortic diameter as well as ascending aortic distensibility (AAD) as described previously.[7]

Analyses were performed by investigators blinded to patients' characteristics and outcomes. Aortic flow measurements were acquired from phase-contrast imaging, and LV SV was determined by integrating the aortic forward flow. Images were acquired in free breathing with prospective electrocardiogram-gating and simultaneous noninvasive BP measurements during flow measurements.

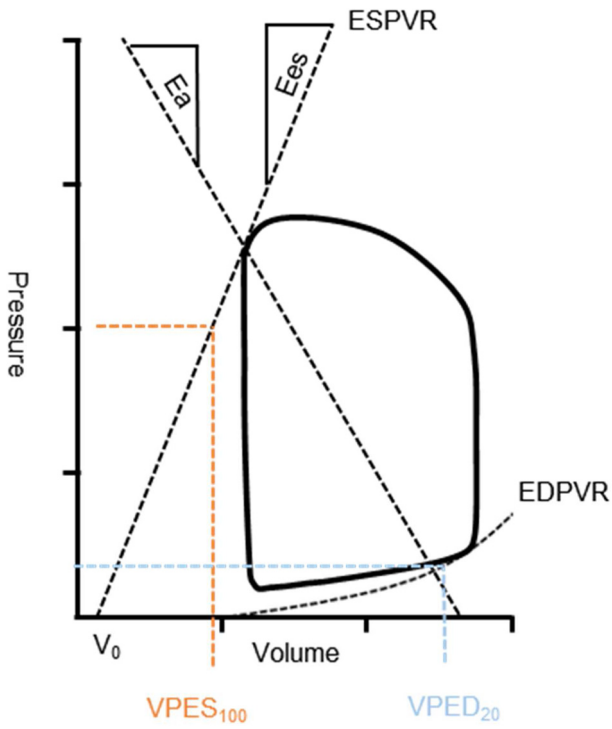

Figure 1. Estimation of different parameters from left ventricular pressure-volume relations. End-systolic, end-diastolic pressure-volume relations (ESPVR and EDPVR) and arterial elastance (E_a) are calculated from single-beat estimations (dotted black lines). E_a is the slope of the line between end-systolic pressure and end-diastolic volume, end-systolic elastance (E_{es}) is the slope of ESPVR. Volume at a normalized end-systolic pressure of 100 mm Hg ($VPES_{100}$) is derived from ESPVR (orange lines) and volume at a normalized end-diastolic pressure of 20 mm Hg ($VPED_{20}$) is derived from EDVPR (blue lines).

RDN Procedure

RDN was performed according to standardized protocols as described previously.[11-13] In brief, repeated ablation runs were delivered to each renal artery. The ablation regions were placed circumferentially to the renal artery wall from distal to proximal. All patients received intravenous remifentanil to control visceral pain.

Statistical Analysis

Normal distribution was tested using Kolmogorov-Smirnov tests. Student's t-tests, Mann-Whitney U tests, or Wilcoxon tests were used to compare continuous variables as appropriate. Dichotomous variables were compared using chi-square tests or McNemar tests. Continuous variables are presented as mean and standard deviation, and dichotomous variables are presented as numbers and percentage.

An analysis of covariance was calculated for differences in ESPVR between NEF and HEF by including E_{es} before and after RDN as dependent variable, V_0 as covariate, and NEF/HEF status as co-factor as proposed by Burkhoff et al.[14]

All statistics were calculated using SPSS 28.0.0.0 (IBM, New York).

Results

Ninety-nine patients with HFpEF were available for analysis.[7] Of these, 36 were classified as having NEF and 63 as having HEF.

Clinical Characteristics and BP

Clinical baseline characteristics were balanced between the groups except for higher baseline BP values in the NEF group (Table 1). Also, baseline creatinine values were higher in patients with NEF without significant differences in estimated glomerular filtration rate.

At follow-up, systolic and diastolic 24 h BP values from ambulatory blood pressure monitoring were significantly reduced (by 8 ± 12 and 5 ± 8 mm Hg, $p < 0.001$ for both) without significant differences between the groups.

NYHA functional class was significantly improved in the overall cohort ($p < 0.001$) without any significant difference between patients with NEF and HEF (Figure 2).

NT-proBNP was higher in patients with NEF compared with patients with HEF (751 ± 989 vs. 449 ± 487 ng/L, $p = 0.03$). NT-proBNP was reduced significantly in both groups (by 145 ± 342 and 74 ± 233 ng/L, $p < 0.05$ for both), without any significant difference in the amount of change at follow-up between the groups ($p = 0.79$).

Arterial Properties

At baseline, E_a did not differ significantly between the groups (Table 2). E_a was reduced significantly at follow-up (−0.2 ± 1.0 mm Hg/mL, $p = 0.02$), without differences between patients with HEF and NEF.

In the subgroup of patients undergoing CMR ($n = 49$), AAD did not differ between the groups at baseline. AAD was significantly increased for the overall cohort (from 1.7 ± 0.8 to 2.2 ± 1.1 × 10^{-3} × mm Hg^{-1}, $p < 0.01$) without between-group differences (Δ 0.5 ± 1.1 in both groups, $p = 0.94$).

Ventricular Properties

At baseline, patients with HEF were characterized by lower ESV, EDV, $VPES_{100}$, and $VPED_{20}$ and a higher E_{es}, as well as lower P_{es} when compared with NEF (Table 2).

At follow-up, EF, E/E′, E_a, E_{es}, and P_{es} were significantly reduced for the overall cohort, whereas ESV, $VPED_{20}$, and $VPES_{100}$ increased. Although P_{es} was reduced in both groups, E_{es} was reduced in patients with HEF but not in individuals with NEF. ESV increased in patients with HEF (by 7 ± 11 mL, $p < 0.01$) but was unchanged in patients with NEF, whereas $VPES_{100}$ increased in both groups. $VPED_{20}$ was increased (by 7 ± 25 mL, $p = 0.02$) with HEF but not with NEF (Table 2 and Figure 3).

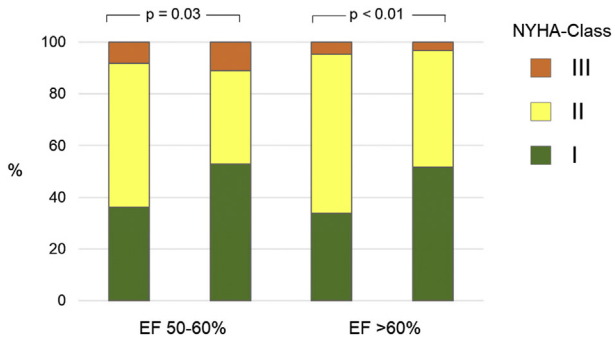

Figure 2. NYHA functional class at baseline and follow-up in patients with normal vs. hypercontractile ejection fraction.
Abbreviations: EF, ejection fraction; NYHA, New York Heart Association.

Ventricular-Arterial Coupling

VAC was significantly lower in patients with NEF when compared with HEF (0.95 ± 0.22 vs. 1.15 ± 0.27, $p < 0.001$, Table 2). At follow-up, VAC was significantly increased in NEF and tended to be lower in HEF without reaching statistical significance.

Discussion

Our findings (a) support the previously postulated concept of fundamentally different phenotypes of HFpEF in patients with high EF in HEF compared with those with NEF; (b) show common beneficial effects of RDN in both groups; and (c) identify different responses of the heart and vasculature to RDN.

When compared with NEF, HEF is characterized by (1) a smaller LV cavity with increased contractility as indexed by lower $VPES_{100}$ and higher E_{es}, (2) a leftward shifted EDPVR as evidenced by a lower $VPED_{20}$, and (3) better VAC. This is in line with recent findings of a study from our group using invasive pressure-volume loop measurements to describe different phenotypes of HFpEF across the range of EF.[3] Therein, patients with HEF were also characterized by a different collagen pattern, higher preload sensitivity, and an impaired contractile reserve, despite more fibrotic areas in patients with NEF.

This might have therapeutic implications as suggested by the accumulating recent evidence on the absence of a uniform treatment response in HFpEF patients with higher and lower EF.[15] This is exemplarily

Table 1
Clinical baseline characteristics and medication

Clinical characteristics	EF (50%-60%; $n = 36$)	EF (>60%; $n = 63$)	p-value
Age (y)	65.8 ± 9.1	65.4 ± 8.5	0.83
Body mass index (kg/m^2)	32.2 ± 5.8	31.0 ± 4.5	0.24
Female, n (%)	9 (25)	25 (40)	0.14
NYHA Class			0.71
I	13 (36)	21 (33)	
II	20 (56)	38 (60)	
III	3 (8)	3 (5)	
Serum creatinine (μmol/L)	92.0 ± 29.7	85.6 ± 26.0	0.04
eGFR (mL/min)	68.5 ± 26.3	76.7 ± 26.3	0.14
Diabetes, n (%)	21 (58)	37 (59)	0.97
Peripheral arterial disease, n (%)	6 (17)	7 (11)	0.43
Coronary artery disease, n (%)	14 (39)	26 (41)	0.82
Previous stroke, n (%)	2 (5)	3 (5)	0.86
Previous myocardial infarction, n (%)	6 (17)	8 (13)	0.59
Atrial fibrillation, n (%)	9 (25)	9 (14)	0.18
Dyslipidemia, n (%)	29 (81)	49 (78)	0.75
24-h systolic blood pressure (mm Hg)	155.2 ± 13.8	148.3 ± 11.2	0.01
24-h diastolic blood pressure (mm Hg)	85.1 ± 11.6	79.3 ± 10.6	0.05
Number of antihypertensive drug classes	5.5 ± 1.4	4.9 ± 1.5	0.26
NT-proBNP (ng/L)	751 ± 989	449 ± 487	0.03

Abbreviations: EF, ejection fraction; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association.

Table 2
Echocardiographic parameters, results from single-beat estimation and changes at follow-up

Parameter	EF 50-60% (n = 36)	Δ Follow-up	p-value (pre vs. post)	EF > 60% (n = 63)	Δ Follow-up	p-value (pre vs. post)	p-value (EF >60% vs. 50%-60% baseline)	p-value (ΔEF >60% vs. ΔEF 50-60%)
EF (%)	58 ± 3	−1 ± 7	0.43	67 ± 4	−4 ± 7	<0.01	<0.01	0.03
E/E'	15 ± 6	0 ± 3	0.39	14 ± 7	−1 ± 5	0.06	0.07	0.60
LVMI (g/m^2)	112 ± 30	−2 ± 36	0.80	112 ± 29	−3 ± 20	0.35	0.99	0.87
EDV (mL)	130 ± 36	−2 ± 19	0.58	108 ± 32	5 ± 25	0.10	<0.01	0.15
ESV (mL)	55 ± 16	1 ± 12	0.71	36 ± 12	7 ± 11	<0.01	<0.01	0.01
SV (mL)	75 ± 21	−3 ± 14	0.25	72 ± 22	−2 ± 20	0.43	0.60	0.86
E_a (mm Hg/mL)	2.5 ± .9	−0.2 ± 0.7	0.07	2.5 ± 1.0	−0.2 ± 1.1	0.10	0.89	0.90
E_{es} (mm Hg/mL)	2.3 ± 1.0	−0.1 ± 0.8	0.54*	2.9 ± 1.3	−0.4 ± 1.2	<0.01*	0.03*	0.06*
P_{es} (mm Hg/mL)	164 ± 22	−18 ± 22	<0.01	155 ± 19	−8 ± 28	0.03	0.03	0.05
EDP	21.1 ± 3.5	−0.2 ± 1.9	0.39	20.1 ± 4.1	−0.7 ± 2.7	0.06	0.07	0.60
E_{es}/E_a	0.95 ± 0.22	0.08 ± 0.20	0.05	1.15 ± 0.27	−0.06 ± 0.26	0.07	<0.01	0.02
$VPES_{100}$ (mL)	23 ± 17	12 ± 16	<0.01	17 ± 14	5 ± 18	0.05	0.04	0.07
V_{0ESPVR} (mL)	−26 ± 23	−9 ± 26	0.12	−24 ± 20	−2 ± 19	0.64	0.91	0.08
$VPED_{20}$ (mL)	124 ± 34	2 ± 18	0.65	106 ± 32	7 ± 25	0.02	0.01	0.24

Abbreviations: E_a, arterial elastance; EDP, end-diastolic pressure; EDV, end-diastolic volume; E_{es}, end-systolic elastance; EF, ejection fraction; ESV, end-systolic volume; LVMI, left ventricular mass index; P_{es}, end-systolic pressure; SV, stroke volume; V_{0ESPVR}, volume axis intercept for linear end-systolic pressure-volume relation; $VPED_{20}$, volume at normalized end-diastolic pressure of 20 mm Hg; $VPES_{100}$, volume at normalized end-systolic pressure of 100 mm Hg.
* p-values from analyses of covariance.

illustrated by the recent findings of the EMPEROR-Preserved Trial. Despite an encouraging overall reduction of clinical events using sodium glucose linked transporter 2 inhibitors, there was no significant effect in the subgroup of patients with an EF >60%.[1]

In contrast to the latter trial, overall beneficial changes can be observed after RDN treatment in HFpEF: both groups gain a similar BP response and an increase in aortic distensibility. Lowering BP is generally associated with a reduced risk for clinical events at follow-up in patients with arterial hypertension.[16,17] Notably, our study cohort consists of patients with uncontrolled and mostly treatment-resistant arterial hypertension on an average of 5 antihypertensive drug classes. In these patients, evidence-based and clinically effective treatment options for BP reduction are rare, which usually results in poor cardiovascular outcome.[18] Although effects of BP control on mortality in HFpEF have not been proven yet, data from smaller studies suggests improved outcome with antihypertensive treatment,[19] and current guidelines support optimal treatment of hypertension in HFpEF.[2]

In line with a previous retrospective study,[20] both groups show an increased AAD at follow-up, likely through a lower sympathetic tone after RDN.[21] It is well known that low AAD is associated with an increase in cardiovascular events at follow-up.[22] Thus, restoring distensibility could further improve prognosis after RDN. These findings warrant confirmation in an adequately powered, controlled study.

An impaired aortic distensibility has been found to be associated with impaired oxygen uptake and exercise capacity in patients with HFpEF.[23] As we and others hypothesized before, this is most likely related to an adverse ventricular-arterial interaction.[7,24] Although lacking a control group, the overall effects observed on BP are encouraging for the potential to improve clinical outcomes.

In addition to common responses after RDN, we observed differences between the 2 groups of EF: In HEF, but not in NEF, E_{es} was reduced, and $VPED_{20}$ increased at follow-up as an expression of a rightward shift of the EDPVR. In our recent study, HEF was also characterized by higher contractility at rest but lower contractile reserve under isometric exercise.[3] LV-EDPVR and contractility both are elevated on sympathetic activation.[25,26] Hypothetically, RDN leads to reversal of these sympathetic-driven components to systolic and diastolic stiffness on a cellular level, for example, by affecting Ca-channel and myosin chain expression or myocardial structure.[27-29]

In contrast to HEF, in NEF, we observed predominantly beneficial effects on VAC and afterload-reduction after RDN. Increasing E_{es}/E_a toward a balanced ratio of 1:1 or 2:1 leads to optimization of mechanical and metabolic efficiency, respectively.[30]

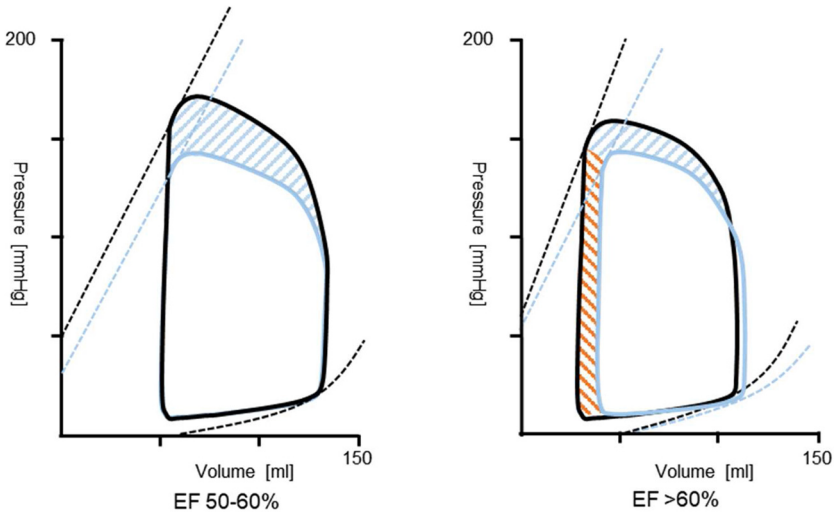

Figure 3. Schematic effects of sympathomodulation using renal denervation (RDN) on averaged pressure-volume relations in patients with normal ejection fraction (EF) (left) vs. high ejection fraction (right). Reduced excess pressure (blue-shaded area) in both groups and reduced hypercontractility (orange-shaded area) in patients with high ejection fraction. Black, pressure-volume loop at baseline before RDN; blue, after RDN.

Limitations

First, as an uncontrolled, retrospective subanalysis of a previous single-center study, the character of the present study is hypothesis-generating only. Second, as we used estimates of pressure-volume relations only, the results may be different on invasive assessment. However, as the approximation methods used herein have been validated before and have been used in various publications, we believe these methods are robust enough for the conclusions of our study. Also, the single-beat estimation method neglects pulsatile components of ventriculoarterial interaction. Thus, the results might differ when assessing and accounting for these components. Third, the definition for heart failure used in our previous and the present study was based on retrospective assignment of the ESC 2016 Guideline criteria for HFpEF. Although this is in line with the identification of patients at elevated cardiovascular risk with the necessity for advancing therapeutic options, the results may differ when applying different noninvasive or invasive definitions of heart failure and enrolling patients in a prospective manner.

Conclusions

Our findings are consistent with the notion that there are at least 2 different hemodynamic phenotypes of HFpEF. Beneficial, although slightly different effects of RDN were observed in both groups. This supports further investigation of sympathetic modulation as a treatment for HFpEF, regardless of EF.

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Ethics Statement

The study was performed in accordance with the Declaration of Helsinki and relevant ethical guidelines.

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Disclosure statement

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