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Electro convulsive therapy: Modification of its effect on the autonomic nervous system using anti-cholinergic drugs

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A B S T R A C T

The antidepressant efficacy of electroconvulsive therapy (ECT) is correlated to the quality of the seizure as measured by EEG but has also been linked to the magnitude of changes in hemodynamic variables. Muscarinic receptor antagonists are frequently used in the treatment, and are known to affect the hemodynamic response. We hypothesized that atropine and glycopyrrolate alter the hemodynamic and autonomic hormonal response to ECT. In a randomized, cross-over study design 23 patients received either atropine, glycopyrrolate or placebo before ECT. Hemodynamic variable, EEG and EMG, and blood adrenaline, noradrenaline and pancreatic polypeptide was determined. No geriatric patients were included. Hemodynamic changes with ECT can be divided into three phases: Drop in blood pressure and pulse rate in 1st post-stimulus phase was less when using 1 mg atropine. In 2nd post-stimulus phase atropine gave a higher systolic blood pressure. No differences were seen in hormone levels after ECT in the three interventions. A significant longer tonic clonic seizure was seen in the glycopyrrolate group and a tendency of the same was seen with atropine. The study found that the changes in hemodynamic variables induced by ECT can be altered by concomitant administration of muscarinic receptor antagonist.

1. Introduction

Electroconvulsive therapy (ECT) is an effective treatment of severe affective illness, but the "quality" of the seizure seems to be predictive for the outcome of the treatment. Its mechanisms of action are still debated and several physiological alterations have been described. ECT has long been known to affect the autonomic nervous system (Gravenstein et al., 1965; Mann et al., 1990). Studies have analyzed the hemodynamic and hormone alterations, with both intentions to describe the treatment and to improve dosing for the patient (Azuma et al., 2007; Bär et al., 2010; Saravanan et al., 2002; Swartz, 2000; Swartz and Shen, 2007). The course of the hemodynamic changes following the electroconvulsive stimulus has previously been described in humans with a bradycardia or even a short asystole directly after the stimulus, presumably caused by activation of the vagal nerve (Bhat et al., 2002; Stewart et al., 2011) which is followed by a period of accelerated heart rate (Nagler, 2013). A more detailed description of the hemodynamic response in humans has been sparse, and only a few blood pressures and pulse recordings have been presented. However, this could be of importance, as a correlation between the hemodynamic impact and treatment has previously been described (Minelli et al., 2016; Saravanan et al., 2002). Two antimuscarinic drugs atropine and glycopyrrolate are commonly employed during ECT. Since only – atropine – crosses the blood brain barrier, they might differentially affect the seizure quality especially the hemodynamic and autonomic hormonal response.

Our aim of the study is to describe the hemodynamic response, the correlations among these parameters and how atropine and glycopyrrolate modifies the response to ECT treatment.

2. Method

The study had been approved by the Regional Ethical committee of Region Copenhagen (p.no. H-4-2012-117). Inclusion criteria were treatment with bilateral ECT. Exclusion criteria included diabetes, arterial hypertension, age above 65 and prior heart diseases (see Table 1 for details).

We applied a randomized, cross-over study design. Hence, in randomized order, all patients received a dose intravenously of either atropine (1 mg), glycopyrrolate (0.2 mg) or saline at three independent ECT sessions. The dosing of atropine and glycopyrrolate was determined by the in-house standard. All patients received thiopental and

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Table 1
Baseline variables.

Subjects[a]	23
Age[b]	42 ± 14 (20–65)
Sex M/F[a]	
Men	13 (57%)
Women	10 (43%)
Diagnosis	
Bipolar affective disorder (F31)	7 (32%)
Depressive episode (F32)	2 (9%)
Recurrent depressive disorder (F33)	12 (55%)
Persistent affective disorder (F34)	1 (5%)

[a] Values are absolute numbers (*relative frequency*).
[b] Values are mean ± sd range).

succinylcholine for induction of anesthesia and muscles relaxation. Doses were determined by a trained anesthesiologist according to local standards.

23 patients admitted to the Psychiatric Center at the Copenhagen University Hospital between October 2012 and August 2013 were recruited to the study after informed consent. 13 were male (57%) and mean age was 42 (standard deviation 14, range 20–65)

Markings were made when the patients were ready for treatment, on the infusion of anesthesia and on the onset of ECT. A blood sample was taken from a cubital vein before anesthesia and five minutes after the onset of ECT. Blood samples were taken in pre-cooled K_2-EDTA sample tubes that were kept on ice immediately after taking the sample. No longer than 30 min after taking the samples, plasma was separated from the blood using a centrifuge at 4000 rpm for 9 min. ECT stimulus, electromyography (EMG) measured with surface electrodes and a 2-channel electroencephalography (EEG) monitoring with fronto-mastoidal placed electrodes was made with a Thymatron apparatus (Thymatron System IV, Somatics, IL, USA).

We used a Finometer device (Finometer Pro, Finapres Medical Systems, The Netherlands) for beat-to-beat non-invasive measurements of heart rate, arterial blood pressure, cardiac output and peripheral vascular resistance (Imholz et al., 1988; Jansen et al., 2001; Schutte et al., 2004; Wesseling, 1996). The cuff was attached to the second or third finger on the patient's right hand soon after arrival to the ECT treatment room, and measurements were continued for 15 min after the termination of the ECT patient. A sandbag and a foam ramp held the arm at heart level, all held together with a Velcro band to minimize motor disturbances to the recordings.

2.1. Data acquisition

Based on the recording of heart rate in pilot trials, four phases of the hemodynamic response were defined: (1) Baseline (2) Pre-stimulus phase (3) 1st post-stimulus phase (4) 2nd post-stimulus phase. Baseline measurement was found between marking of “patient ready” and “onset of anesthesia”. Pre-stimulus phase was defined as a mean of measurement in the period 100–105 s after infusion of anesthesia. This specific time was chosen as pilot studies revealed this was the time needed for the anesthesia be sufficient for the ECT treatment. Since the Finometer Pro device is able to measure the arterial pressure of the systole and diastole of each heartbeat 1st post-stimulus phase was defined as the hemodynamic variables recorded together with the minimum systolic pressure immediately after ECT stimulation. 2nd post-stimulus phase was defined as an average of measurements around the peak systolic pressure heart beat at an interval of +− 2.5 s. The peak systolic pressure had to be within 30 s after electric stimulation (see Fig. 1 for graphic illustration). Analysis of the hemodynamic parameters measured by the Finometer Pro was made with the Beatscope 1.1a software program (Finopres Medical Systems, The Netherlands).

2.2. Analysis of catecholamines

Norepinephrine and epinephrine used as standards were obtained from Thermo Fisher Scientific (MA, USA). The water was obtained from a Milli Q water purification system (Millipore, MA, USA). The Acetonitrile were chromatography grade (Merck, Darmstadt, Germany). All other chemicals (Merck or Fluka Chemie AG, Buchs, Switzerland) were of analytical grade or better and were used as supplied. The Thermo Scientific Dionex Plasma Catecholamine analysis kit was used for extraction from human plasma. 1 mL plasma and 50 µL internal standard 10 ng/mL dihydroxybenzylamine (DHBA) was added to the extraction tube and was mechanically rocked for 10 min. The alumina was allowed to settle and the supernatant was aspirated and discarded, followed by twice adding a 2.5 mL wash solution with a repeated supernatant aspiration and discarding. 200 µL of eluting solution buffer was added to the tube and mixed for 10 min. Now the catecholamine's was eluted from the tube and centrifuged for 5 min at 14,000 rpm and supernatant water was removed (Eriksson and Persson, 1982; Hjemdahl, 1984; Koch and Polzin, 1987).

The concentrations of DHBA, dopamine, norepinephrine and epinephrine were determined by HPLC with electrochemical detection (8). The column was a HR-80 C18 (4.6 mm × 80 mm, particle size 3 µm, Thermo Scientific). The mobile phase consisted of 55 mM sodium acetate, 1 mM octanesulfonic acid, 0.1 mM Na_2EDTA and 8% Acetonitrile, adjusted to pH 3.2 with 0.1 M acetic acid, and was degassed using an on-line degasser. Twenty µL of the samples was injected and the flow rate was 0.15 mL/min. The electrochemical detection was accomplished using an amperometric detector (Antec Decade from Antec, Leiden, The Netherlands) with a glassy carbon electrode set at 0.8 V, with an Ag/AgCl as reference electrode (Wang and Hutchins, 1985). The output was recorded on a computer program LC solution from Shimadzhu (Shimadzu Corp., Kyoto, Japan), which also was used to calculate the peak areas.

2.3. Analysis of pancreatic polypeptide

Pancreatic polypeptide analysis was made by using a human pancreatic polypeptide ELISA kit (EZHPP40K, Merck Milipore, Germany). The standard protocol from the company was used. The water was obtained from a Milli Q water purification system (Millipore, MA, USA). Absorption readings were made with the use of a spectrophotometer (Powerwave HT Microplate Spectrophotometer, Biotek, USA). Concentrations were calculated with a 4-parametric logistic regression using the web service on www.elizaanalysis.com/app.

2.4. Statistical analysis

The software program R version 3.02 was used for statistical analysis with the additional packages “nlme”, “Skillings.Mack”, “coin” and “ggplot2” attached.

For the main longitudinal analysis, linear mixed effects models were used because of several data points over time in each subject within each of the three treatments. The default settings of the “lme” functions within the “nlme” package was used. These include fitting with restricted maximum likelihood and an unstructured covariance model. Models were constructed with time, treatment and treatment order as fixed effects and subject as a random effect on the intercept. Due to missing values we used a Skillings–Mack statistic (sms) with Monte Carlo simulation on *p*-values for supplementary analyses of differences between interventions at specific time points. For post hoc analysis we performed a pairwise comparisons using Wilcoxon rank sum test with a Bonferroni adjustment of *p*-values due to multiple comparisons. Models were validated by visual assessment of residual distribution with QQ-plots and fitted vs standardized residuals as well as influence analysis by Cook's diagrams. All models were deemed to adhere to the principles of homoscedasticity. *P*-values below 5% were regarded as statistically

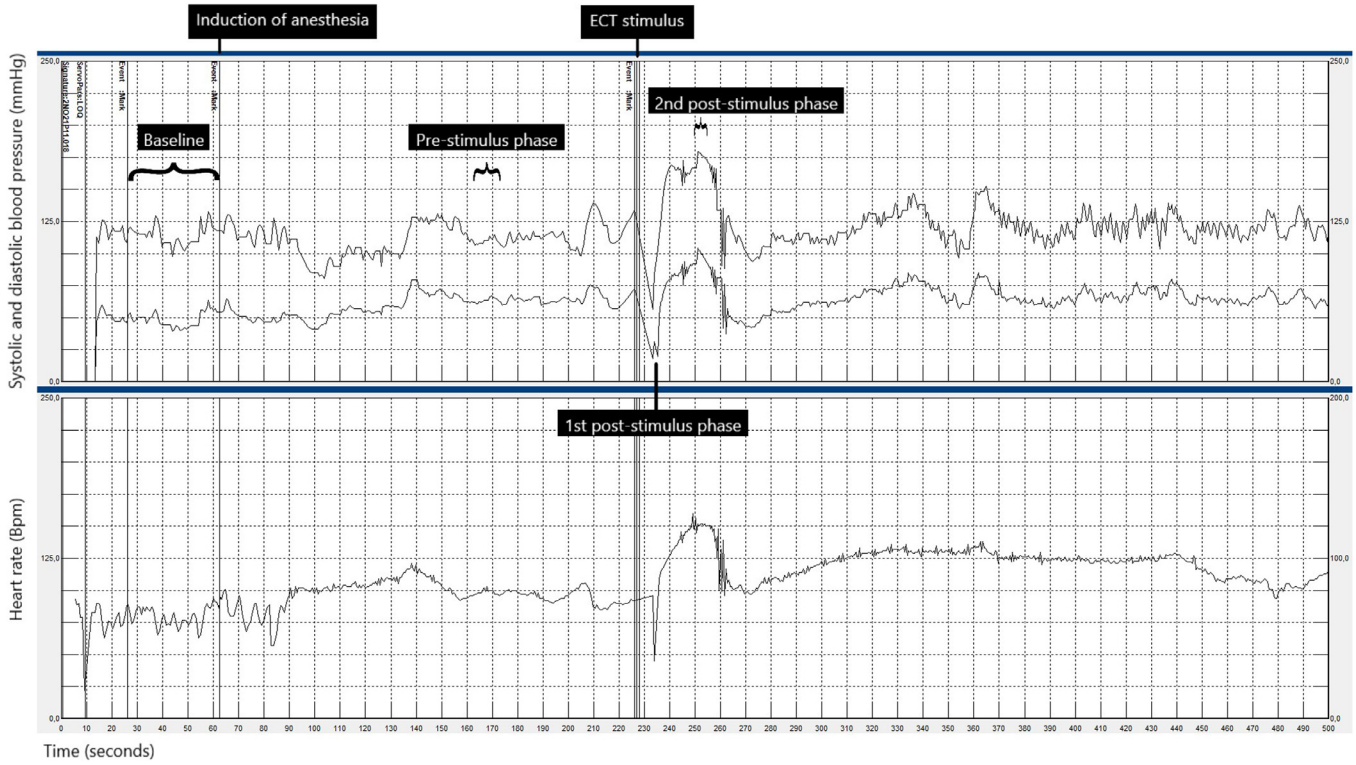

Fig. 1. Representative sample of continuous reading of systolic and diastolic pressure in upper graph, corresponding reading of heart rate in lower graph. ECT phases are illustrated on upper graph.

significant and consequently 95% confidence intervals are reported.

All boxplots represented shows the median value, the upper (75%) and lower (25%) quartile and whiskers shows the inter quartile range multiplied with 1.5.

3. Results

Due to motor disturbances during the stimulus period of the treatment, some recordings are missing in the ECT phases, or too many artefacts made them unreliable. Some recordings are missing the Pre-ECT phase, from when the treating team gave the stimulus earlier than 100 s after infusion of anesthesia. There was no statistical difference in the intervention order when comparing the intervention groups after having removed drop out values.

A summary of the measured variables is shown in Table 2

3.1. Thymatron setting and anesthesia doses

The anesthesiologist was allowed to make adjustments in medication used to anesthetize the patient, so that some patients receive alternating medication doses in the study. The median dose of thiopental was 250 mg (range 200–550 mg), of suxamethonium 50 mg (range 40–75 mg). Chlorprothixen were used for pre-medication according to in-house standard. No significant differences were found regarding the dosing of anesthesia or pre-medication with chlorprothixen when comparing the study data grouped according to the intervention. In the same manner, the psychiatrist was allowed to adjust the setting of the Thymatron device. No significant differences were found in the three groups when comparing setting of the Thymatron apparatus.

3.2. Heart rate, blood pressure and cardiac output

3.2.1. Baseline

Values showed no significant difference between the three interventions in the study.

3.2.2. Pre-stimulus phase

In the pre-stimulus phase a raise in pulse and a transient drop in blood pressure (Fig. 1) followed by a raise in systolic and diastolic blood pressure were seen in all three interventions but with no significant difference between the interventions for heart rate (sms = 0.21, $p = 0.92$), systolic blood pressure (sms = 0.68, $p = 0.709$), diastolic blood pressure (sms = 0.39, $p = 0.821$) or cardiac output (sms = 0.51, $p = 0.800$).

3.2.3. 1st post-stimulus phase

The drop in heart rate compared to baseline was 25 beats/min less with atropine treatment compared to placebo (CI95: 7–43, $p = 0.01$) whereas the difference between glycopyrrolate treatment and placebo was 0 (CI95: −16 – 16, $p = 0.96$). The variance of heart rate between interventions were significant different (sms = 6.52, and $p = 0.033$) with a pairwise Wilcoxon test showing a significant difference between atropine and placebo ($p = 0.007$), atropine and glycopyrrolate ($p = 0.009$) whereas there was no significant difference between glycopyrrolate and placebo ($p = 1.000$). Systolic blood pressure decreased by 24 mmHg with placebo treatment between baseline and 1st post-stimulus phase (CI95: 8–41, $p = 0.004$). The general variance of systolic blood pressure in the three treatment arms was insignificant (sms = 3.00, $p = 0.221$), although atropine showed a borderline-significant diminishment of drop in systolic blood pressure ($p = 0.062$). No significant variance of diastolic blood pressure between the three interventions was found (sms = 5.25, $p = 0.072$). All intervention arms had a drop in CO in 1st post-stimulus phase; CO decreased with −4,3 L/min in the placebo group (CI95: −5.6 – −3.1, $p = < 0.0001$) compared to baseline values. There was a significant difference in the general variance between the three interventions (sms = 6.75, $p = 0.030$). A pairwise Wilcoxon test showed a significant difference between atropine and glycopyrrolate ($p = 0.027$), but non-significant between atropine and placebo ($p = 0.106$) and glycopyrrolate and placebo ($p = 1.000$).

Table 2
Summary statistics of measured variables.

Variable	Time	Placebo	Atropine	Glycopyrrolate
Heart rate (BPM)[a]	Baseline	87 ± 13 (67–113)	87 ± 15 (62–114)	85 ± 15 (63–119)
	Pre-ECT	101 ± 13 (73–118)	103 ± 12 (75–119)	99 ± 15 (76–128)
	1st ECT	50 ± 20 (23–97)	77 ± 24 (42–115)	49 ± 21 (24–113)
	2nd ECT	139 ± 16 (118–160)	144 ± 17 (124–168)	137 ± 18 (88–163)
Cardiac output (L/min)[a]	Baseline	7.3 ± 2.1 (4.0–12.6)	7.0 ± 2.2 (3.6–11.0)	7.2 ± 2.0 (3.6–10.6)
	Pre-ECT	6.1 ± 2.3 (2.7–12.0)	6.1 ± 2.5 (2.7–12.0)	5.7 ± 2.1 (1.5–9.2)
	1st ECT	3.1 ± 2.0 (0.3–5.8)	5.1 ± 2.8 (1.2–10.0)	2.7 ± 1.1 (1.3–4.5)
	2nd ECT	8.3 ± 3.6 (1.6–14.2)	7.9 ± 6.8 (1.7–26.0)	8.5 ± 3.6 (4.3–18.9)
Systolic BP (mmHg)[a]	Baseline	122 ± 17 (91–174)	125 ± 16 (96–158)	123 ± 15 (96–146)
	Pre-ECT	126 ± 29 (86–184)	133 ± 37 (60–200)	129 ± 30 (70–186)
	1st ECT	97 ± 34 (51–147)	130 ± 24 (102–171)	105 ± 32 (55–168)
	2nd ECT	146 ± 42 (69–201)	169 ± 30 (115–204)	165 ± 32 (95–222)
Diastolic BP (mmHg)	Baseline	69 ± 13 (37–88)	73 ± 11 (53–93)	70 ± 9 (53–83)
	Pre-ECT	81 ± 17 (54–123)	86 ± 21 (43–127)	84 ± 17 (49–120)
	1st ECT	53 ± 26 (18–91)	79 ± 20 (41–116)	64 ± 25 (19–105)
	2nd ECT	90 ± 27 (34–121)	111 ± 25 (64–142)	106 ± 26 (54–152)
Peripheral Seizure length (seconds)[a]	Ictus	25 ± 14 (5–59)	33 ± 15 (10–66)	37 ± 22 (5–85)
EEG (seconds)[a]	Ictus	40 ± 25 (20–125)	45 ± 21 (13–99)	45 ± 22 (16–90)
Post-ictal suppression index[a]	Post-ECT	66 ± 24 (18–94)	75 ± 20 (48–99)	74 ± 21 (44–96)
Epinephrine (μg/mL)[b]	Baseline	2.0 $_{IQR}$1.49 (0.32–10.9)	1.8 $_{IQR}$1.19 (0.14–4.8)	2.6 $_{IQR}$1.53 (0.6–9.5)
	Post-ECT	2.2 $_{IQR}$1.29 (0.23–77.1)	2.0 $_{IQR}$1.52 (0.13–4.7)	2.2 $_{IQR}$0.72 (1.32–3.4)
Norepinephrine (μg/mL)[b]	Baseline	8.6 $_{IQR}$6.4 (1.5–27)	10.7 $_{IQR}$7.9 (1.5–21)	10.6 $_{IQR}$9.3 (1.0–141)
	Post-ECT	16.4 IQR12.5 (4.1–147)	13.5 $_{IQR}$7.7 (1.2 −52)	10.1 $_{IQR}$7.4 (2.6–81)
Pancreatic polypeptide (pg/mL)[b]	Baseline	35 $_{IQR}$73 (1.1–221)	46 $_{IQR}$28 (3.2–432)	71 $_{IQR}$208 (0.6–646)
	Post-ECT	120 $_{IQR}$*230 (16.1–669)*	95 $_{IQR}$170 (1.1–463)	72 $_{IQR}$129 (14.5–646)

[a] Values are mean ± sd (range).
[b] Values are median $_{IQR}$interquartile range, (range).

3.2.4. 2nd post-stimulus phase

All three intervention arms showed a raise in both heart rate, blood pressure and cardiac output when compared to 1st post-stimulus phase and baseline levels. There was no significant variation of heart rate between the interventions (sms = 1.69, $p = 0.461$). A general difference was seen in systolic blood pressure between the three interventions (sms = 6.12, $p = 0.04$), but a pairwise Wilcoxon test showed no significant sublevel difference between atropine and placebo ($p = 0.333$), atropine and glycopyrrolate ($p = 1.000$) and glycoyrrolate and placebo ($p = 0.725$). No significant difference in the three interventions was seen in diastolic blood pressure (sms = 4.06, $p = 0.132$) or cardiac output (sms = 3.31, $p = 0.191$).

Figs. 1 and 2 illustrates the hemodynamic changes in the three intervention arms.

3.4. Adrenalin, noradrenalin and pancreatic polypeptide

Measurement of the post-stimulus values adrenalin in the two interventions showed a non-significant mean difference from placebo being 0.21 (CI95: −0.50 – 0.93, $p = 0.55$) and 0.14 μg/L (CI95: −0.65 – 0.93, $p = 0.72$) for atropine and glycopyrrolate respectively. Similar measurements were found for noradrenalin with a non-significant mean difference from placebo being 0.02 (CI95: −4.27 – 4.30, $p = 0.99$) and −2.3 μg/L (CI95: −7.10 – 2.45, $p = 0.33$) for atropine and glycopyrrolate, respectively.

A plotting of the residual values showed a non-normal distribution of the measured values of pancreatic polypeptide, which were solved by a log-transformation of the values. ECT treatment showed a non-significant elevation of the logarithmic value of pancreatic polypeptide in the placebo group of 0.6 (CI95: −0.1 – 1.3, $p = 0.074$), which seemed lessened when atropine or glycopyrrolate was used with no apparent difference among these two interventions. When comparing glycopyrrolate with atropine, no significant difference was found (CI95: −1.2 – 1.1, $p = 0.93$).

Fig. 3 illustrates the hormone changes in the three intervention arms.

3.5. Generalized tonic clonic (GTC) seizure, EEG and post-ictal suppression index

The three intervention groups showed a GTC seizure length of mean 25.1 s (CI95: 17.4–33), 33.0 seconds (CI95: 24.8–41.2, $p = 0.108$) and 37.4 s (CI95: 29.0–45.8, $p = 0.017$) for placebo, atropine and glycopyrrolate respectively.

In entries with glycopyrrolate administered a significant prolongation of 12.3 s of seizures as measured by EMG surface electrodes over the extensor muscles of the forearm. Administration of atropine gave 7.9 s longer seizure, but the finding was non-significant. When comparing glycopyrrolate with atropine, no significant difference was found (CI95: −5.8 – 14.6, p = 0.39). Analysis of variance among the three intervention groups also showed a slight significant difference (sms = 6.12, $p = 0.039$).

A similar but non-significant observation was seen on glycopyrrolate prolonging the length of the EEG measured ictus with 5.5 seconds (CI95: −7 – 18, $p = 0.378$) and atropine with 4.2 s (CI95: −8.1 – 16, $p = 0.494$), both measured by electro encephalogram with frontomastoidal placed electrodes giving a two-channel monitoring. When comparing glycopyrrolate with atropine, no significant difference was found (CI95: −12 – 14.1, $p = 0.84$). Analysis of variance among the three intervention groups also showed no significant difference (sms = 0.506, $p = 0.783$).

The EEG and GTC seizure findings are illustrated in Fig. 4.

Post-ictal suppression index readings showed a mean of 65.5 (CI95: 51–80) in the placebo group and 74.7 (CI95: 58–91, $p = 0.36$) and 74.9 (CI95: 57–93, $p = 0.37$) for the atropine and glycopyrrolate group, respectively. No significant differences were found among the three interventions (sms = 3.09, $p = 0.247$).

4. Discussion

In our continuous monitoring of the patients' hemodynamic parameters we could distinguish 4 periods during the ECT session. These periods have characteristics that suggest a great impact on the autonomous nerve system during the ECT treatment. It has previously been

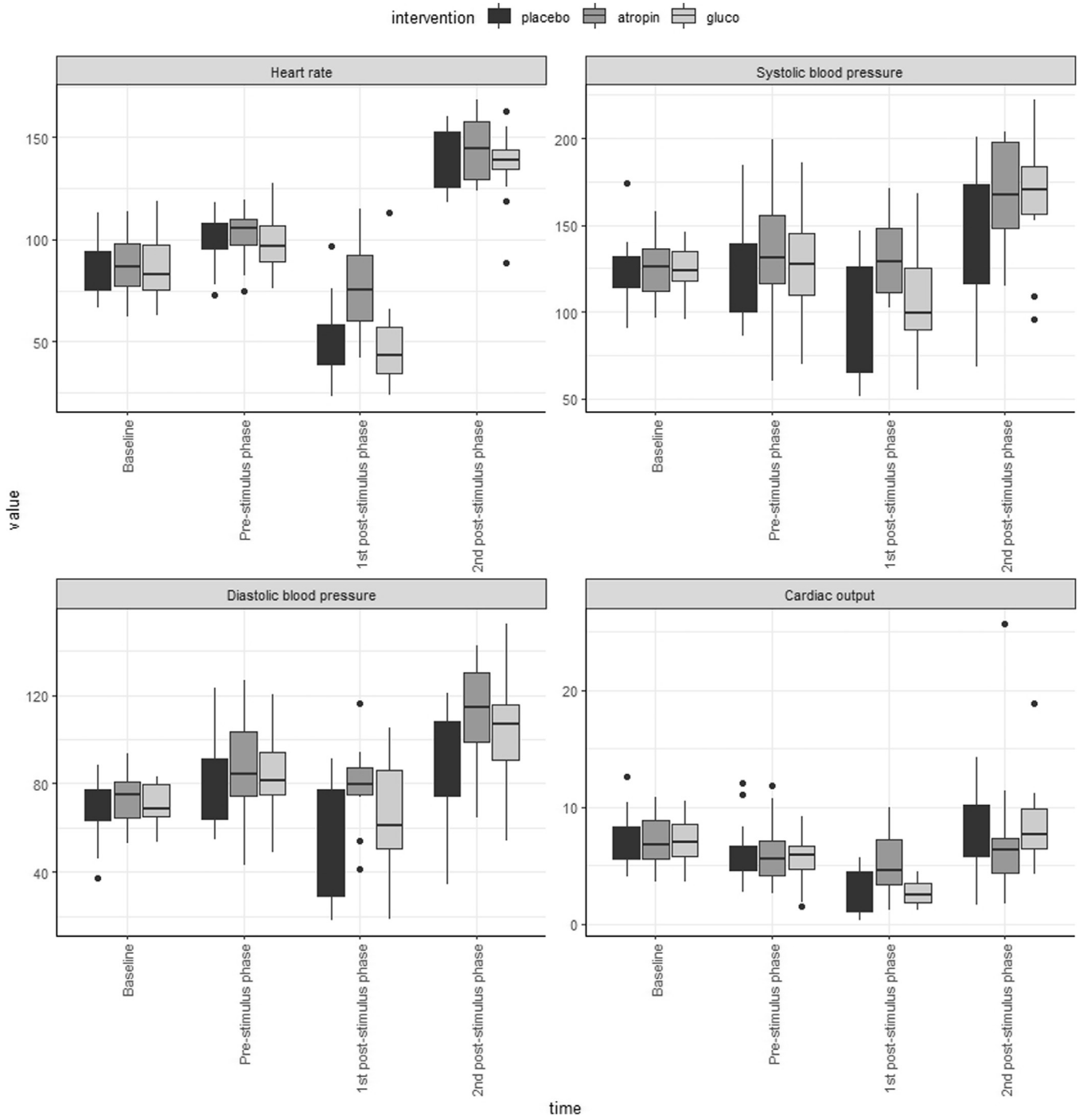

Fig. 2. Boxplots of cardiovascular variables by intervention group measured by the Finometer Pro device. Heart rate measured in beats per minute, blood pressures measured in mmHg, cardiac output measured in liters per minute.

shown in animal studies, that ECT gave rise to biochemical and anatomical alterations in the hypothalamus, striatum and hippocampus area (Hageman et al., 2008; Hjæresen et al., 2008; Landau et al., 2011), thus beyond the reach of scalp EEG monitoring. ECT treatment is usually monitored by measuring the length and quality of EMG and EEG recordings (Fink and Johnson, 1982; Mayur et al., 1999). Previous studies have tried to find other ways to determine if the ECT treatment had a sufficient impact on the patient's depression (Azuma et al., 2007; Minelli et al., 2016; Saravanan et al., 2002). Studies on animals have found, that electric stimulation of the hypothalamus could give sudden tachycardia, hypertension and cardiac arrhythmias (Welch and Drop, 1989). On canine studies, these hemodynamic changes during ECT treatment were suggested to be mediated through the vagal nerve, the sympathetic nerve system and circulating catecholamines (Anton et al., 1977; Colville et al., 1958).

Anti-cholinergic drugs have been shown to block some of the release of pancreatic polypeptide (Bär et al., 2010), although in this study only a trend was found. Neither adrenaline nor noradrenalin showed any alterations when blood levels before ECT and five minutes after were compared. The timing of the blood sampling was chosen to be five minutes after induction of ECT as it had been shown by Bär et al. to give the highest level of pancreatic polypeptide (Bär et al., 2010). It is possible that a different timing would be more suitable for measuring alterations in catecholamine levels. It has previously been found, that

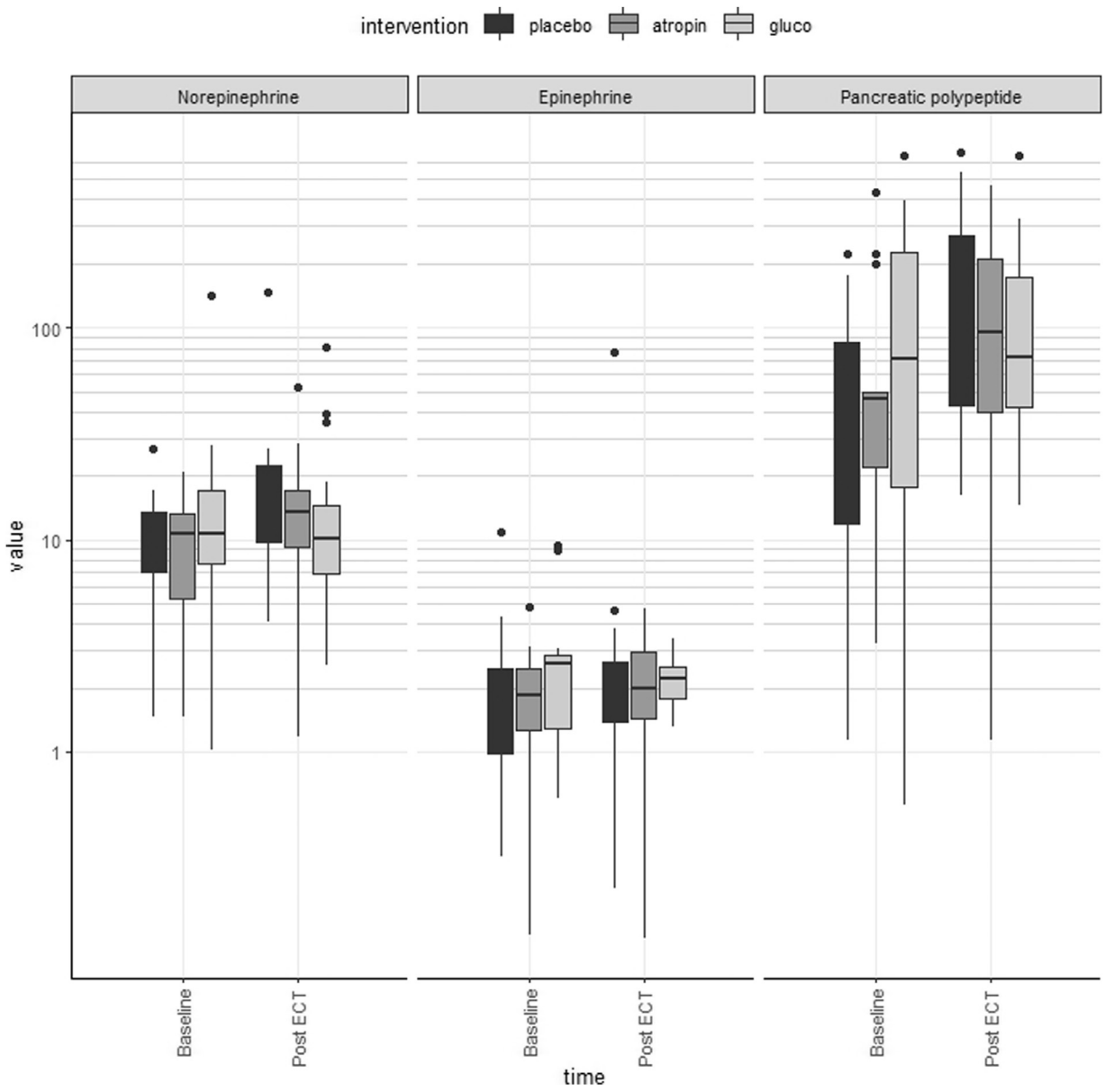

Fig. 3. Hormones before and after ECT, epinephrine and norepinephrine measured in μg/mL, pp = pancreatic polypeptide measured in pg/mL.

levels of both adrenaline and noradrenalin were elevated immediately after shock, and normalized after 10 min (Gravenstein et al., 1965). Studies on plasma norepinephrine half-life showed an average of T½ being 2 min (Esler et al., 1981), and this might be accelerated in patients with affective illness (Esler et al., 1982). However, since we did not duplicate the hormone analyses an intra-assay coefficient could not be estimated and we were therefor not able to assess the repeatability of measurements.

In our study atropine seemed to have a more profound effect on interfering with hemodynamic changes during the ECT treatment than did glycopyrrolate when comparing both to placebo, which could be explained by atropine crossing the blood-brain barrier, which glycopyrrolate, being a quaternary ammonium compound usually does not (Proakis and Harris, 1978). This could, however, be due to a dosing of glycopyrrolate that were not equipotent to that of atropine. We compared 1 mg atropine to 0.2 mg glycopyrrolate which were the in-house standards. A dose of 0.6 mg atropine compared with 0.2 mg has previously showed a comparable antisialogogue effect, but at this dose atropine also showed an induction of a higher heart rate (Greenan et al., 1983), and other studies showed similar findings with glycopyrrolate having more antisialogogue effect compared with atropine, whereas the later induced more tachycardia (Mirakhur and Dundee, 1980; Salem and Ahearn, 1986). Our study supports that administration of atropine adjacent to ECT treatment gives a tendency of a higher heart rate. A previous study of Anastasian et al. (2014) has showed, that this is also seen in lower doses of atropine. It could be speculated, that the higher hemodynamic stress induced by atropine could result in a higher risk of post-ictal arrhythmias, but to the knowledge of the authors no evidence supporting this has previously been described. However, when comparing the results of this study with others, there should be an awareness on the dosing of the catecholamines.

The finding of a significant prolonged GTC seizure in patients given glycopyrrolate was both unexpected and counter intuitive. Glycopyrrolate does not usually penetrate the blood-brain barrier (Proakis and Harris, 1978), although there has been found evidence that ECT can disrupt the blood–brain barrier (Andrade and Bolwig, 2014; Öztas and Carmurcu, 1989). Thus, the prolonging of an activity in the brains motor cortex could involve a biomechanism with glycopyrrolate lowering the seizure threshold. A mechanism could also be a lowering of the pulmonic secretion, which could lead to a lowering of

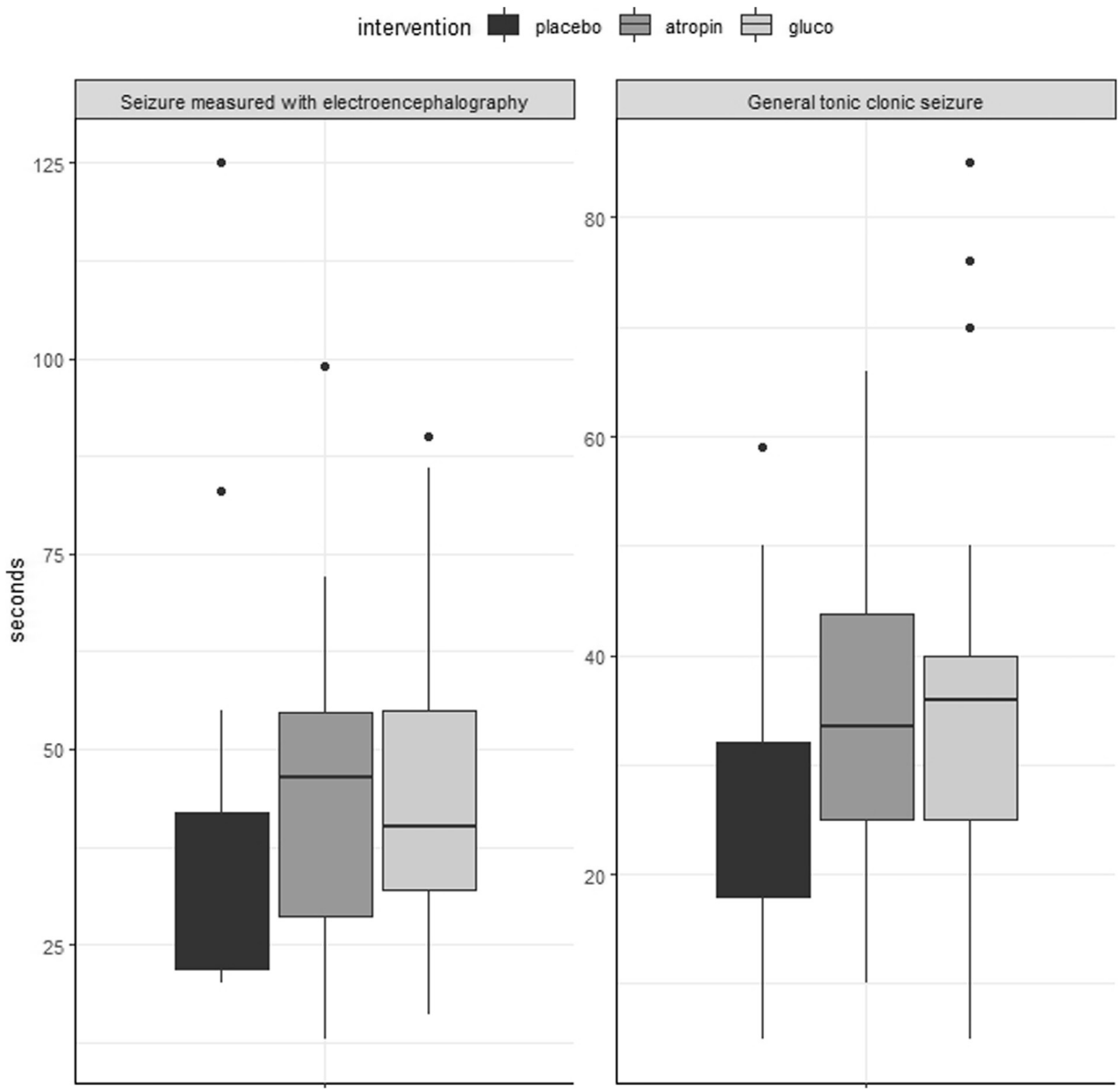

Fig. 4. Duration of paroxystic seizure measured with EEG and EMG.

plasma carbondioxide giving the same effect as hyperventilation prior to ECT in prolonging seizure duration (Gómez-Arnau et al., 2018). A trend towards the same finding was seen in patients given atropine, but this was without statistical significance. More research should be done in this field before conclusions can be made.

The study above is designed to describe the course of hemodynamic changes through continuous measurement throughout the treatment session and hormonal changes, and how the hemodynamic variables and hormonal changes are influenced by concomitant medications commonly used adjacent to the ECT treatment. The hormonal changes at the chosen timepoints did not reveal significant alterations. Future studies on ECT that includes these hemodynamic variables and hormonal changes should be aware of the influence of anticholinergic drugs.

4.1. Conclusion

The magnitude of changes in hemodynamic variables induced by ECT can be changed by concomitant administration of muscarinic receptor antagonist often used in conjunction with the anesthesia. The study found that glycopyrrolate caused a longer length of generalized tonic clonic seizure, which might be an unwanted side effect.

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None of the authors declare any conflicts of interest.

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