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Novel Effects of the Gastrointestinal Hormone Secretin on Cardiac Metabolism and Renal Function

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Running Head: Cardiorenal Effects of Secretin

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Abstract

The cardiac benefits of gastrointestinal hormones have been of interest in recent years. The aim of this study was to explore the myocardial and renal effects of the gastrointestinal hormone secretin in the GUTBAT trial (NCT03290846). A placebo-controlled crossover study was conducted on 15 healthy males in fasting conditions, where subjects were blinded to the intervention. Myocardial glucose uptake was measured with [^{18}F]2-fluoro-2-deoxy-D-glucose ([^{18}F]FDG) positron emission tomography. Kidney function was measured with [^{18}F]FDG renal clearance and estimated glomerular filtration rate (eGFR). Secretin increased myocardial glucose uptake compared to placebo (secretin vs. placebo, mean $\pm$ standard deviation, 15.5 $\pm$ 7.4 vs. 9.7 $\pm$ 4.9 µmol/100g/min, 95% confidence interval (CI) [2.2, 9.4], p=0.004). Secretin also increased [^{18}F]FDG renal clearance (44.5 $\pm$ 5.4 vs. 39.5 $\pm$ 8.5 ml/min, 95%CI[1.9, 8.1], p=0.004) and eGFR was significantly increased from baseline after secretin, compared to placebo (17.8 $\pm$ 9.8 vs. 6.0 $\pm$ 5.2 Δml/min/1.73m^2, 95%CI[6.0, 17.6], p=0.001). Our results implicate that secretin increases heart work and renal filtration, making it an interesting drug candidate for future studies in heart- and kidney failure.

NEW & NOTEWORTHY

Secretin increases myocardial glucose uptake compared to placebo, supporting a previously proposed inotropic effect. Secretin also increased renal filtration rate.

The cardiac benefits of gastrointestinal (GI) peptides have been of great interest in recent years. For the first time in the history of diabetes treatment, type 2 diabetes (T2D) medications have shown benefits in cardiovascular mortality(15). One such drug class is glucagon-like peptide-1 (GLP-1) analogues, but their precise mechanisms for cardiac benefits are still being uncovered(37). Secretin, which belongs in the same family of GI peptides as GLP-1, is the first hormone discovered and with it came the concept of endocrine regulation in the 1920s(4). It is secreted during feeding and its best established effect is induction of pancreatic exocrine secretion(28). We recently showed that secretin is not only a digestive hormone, but also controls appetite and activates meal-associated brown adipose tissue thermogenesis(32, 33). Evidently, secretin has pleiotropic effects, as human secretin receptors are present in multiple organs and tissues, including the heart and kidney(12).

In the early 1980s, intravenous secretin infusion was shown to increase cardiac output and stroke volume in heart failure patients(21) and in patients with angina, but normal ventricular function(22). Since systemic resistance also fell, the secretin induced effect was proposed to be mainly through a decrease in afterload. However, due to the substantial 20 percent increase in cardiac output, the authors speculated that there might also be an increase in myocardial contraction. Since then animal studies have provided support for an inotropic effect(7, 20), but it could not be proven in humans with the previously implemented method. Furthermore, several studies have also indicated that secretin has an effect on fluid homeostasis(9, 11), both centrally and through aquaporin channels in the kidneys, independent of

vasopressin(10). It also increases renal blood flow(59). In earlier clinical studies, secretin was shown to have diuretic effects in humans(3, 56, 57).

Secretin's cardiorenal effects have not been studied in humans with current, state of the art methods. We recently reported the prespecified endpoints of the GUTBAT clinical trial, a randomized placebo-controlled crossover trial examining the effect of secretin on brown adipose tissue and appetite(32). In the present exploratory study, we aimed to investigate the cardiorenal effects of secretin in the participants of the GUTBAT trial (Clinical trial number: NCT03290846).

Materials and Methods

Study subjects

Subjects (n = 16) who filled the inclusion criteria (body mass-index (BMI) 20-26 kg/m^2, male, age 18-65 years, no chronic disease that would affect the outcome) and who presented healthy at the screening visit (according to their medical history, as well as when assessed by their cardiovascular status, standard 2-hour oral glucose tolerance test (OGTT), routine laboratory tests, electrocardiogram (ECG), and blood pressure) were enrolled in the PET/CT study. After one drop-out before the completion of the study, 15 subjects were included in the analysis (mean $\pm$ standard deviation (SD) age 40.9 $\pm$ 12.5 years, median BMI 24.0 $\pm$ 1.9 kg/m^2). Written informed consent was provided by all subjects. All participants were recruited between the years 2016 and 2017. The trial ended when all pre-planned studies were completed (Clinical Trials Number: NCT03290846). No important harms or unintended effects were observed. The study protocol was reviewed and approved

by the Ethics Committee of the Hospital District of Southwest Finland prior to starting the study. The study was performed according to the principles of the Declaration of Helsinki.

Study design

The study was conducted at Turku PET Centre and consisted of two separate [^{18}F]FDG PET scan days after ≥12 hours of fasting. The scans were conducted within the interval of 2-28 days of each other (**Fig. 1**). Subjects were blinded to the intervention and randomized to receive placebo (saline) and secretin (secretin pentahydrochloride 1IU/kg * 2) twice intravenously as a two-minute infusion on different days. Whole body energy expenditure (EE) was assessed with indirect calorimeter (Deltatrac II, Datex-Ohmeda) during the PET-scans(41). Conventional 12-lead ECG was recorded at baseline, at one hour and at two hours. Repeated arterialized venous samples were collected from the antecubital vein during the scanning days.

Scanning protocol

[^{18}F]FDG was produced at the Turku PET Centre, as described previously(23). The two PET/CT scans (GE DiscoveryTM ST System, General Electric Systems, Milwaukee, MI, USA) were conducted according to identical scan acquisition protocols. A two-minute intravenous infusion of saline or secretin was given 20 minutes prior to the administration of 150 MBq of [^{18}F]FDG. Subsequent to the radiotracer injection, a second two-minute infusion of placebo or secretin was initiated. A dynamic PET scan was started simultaneously and acquired on the neck region for 40 minutes (results have been reported previously(32)) and the thoracic

region for 15 minutes (frames: 5 x 3 min) (**Fig. 1**). A low dose CT was conducted before each dynamic PET-scan for attenuation correction and anatomical localization.

Image analysis

Image analysis was conducted with Carimas 2.8 software (Turku PET Centre, Turku, Finland). An automated cardiac analysis tool was used for myocardial time activity curves (TAC). Regional TAC data was then analyzed, taking into account radioactivity in arterialized plasma, by using fractional uptake rate (FUR)(52). Arterialized plasma radioactivity was assessed with an automatic gamma counter (Wizard 1480, Wallac, Turku, Finland). Myocardial glucose uptake (μmol/100g/min) was calculated by multiplying FUR with plasma glucose levels and dividing by tissue density of 1.0298 g/mL(61) and a lumped constant value of 1(8). Brown adipose tissue (BAT) and skeletal muscle glucose uptake was calculated as previously reported (32). Glucose uptake rates of these tissues are also expressed in umol/min, by multiplying for organ mass. For the heart, the reference value of adult males (332 grams) was used (61). BAT mass was measured as previously described (54) and skeletal muscle mass was estimated from age, height, weight and waist circumference as previously described (24).

ECG assessments

Twelve-lead ECGs were recorded prior to scanning, as well as 60 and 120 minutes after the first secretin or placebo dose (**Figure 1**). ECG was recorded using GE Medical Systems MAC 5000 resting ECG analysis system. Heart rate, PR-, QRS and

QT intervals were automatically measured and assessed by a qualified cardiologist. Heart rate corrected QT interval (QTc) was calculated with Bazzett's formula(5).

Indirect calorimetry analysis

Analysis was started from 10 minutes after the first secretin dose. Whole body energy expenditure (EE) and the rate at which carbohydrates (CHO) and lipids (FO) were oxidized for EE, were calculated with Matlab (Version: R2011a), using the Weir equation(60) and the manufacturer's equations(36). Whole body energy expenditure, carbohydrate oxidation and fat oxidation by indirect calorimetry measurements are expressed in kcal/d. Protein metabolism was calculated by assuming urine nitrogen as 13 g/24h(53).

Renal function measurements

Serum samples of the first n=12 scanned subjects were analyzed for a metabolic panel, including creatinine, the Nightingale Health laboratory (Helsinki, Finland), with nuclear magnetic resonance (NMR) spectroscopy(47). Glomerular filtration rate was measured with Cockcroft-Gault equation(13). All subjects voided before start of scan and after the scan. Times were recorded and urine volumes measured. Subjects received a slow saline infusion (NaCl0.9) during the scan for sampling purposes and infusion volumes were not controlled. Urine radioactivity was assessed with an automatic gamma counter at the end of the scan (Wizard 1480, Wallac, Turku, Finland). [^{18}F]FDG renal clearance rate (n=15) was calculated as previously described, with urine activity (FDG_{urine}) divided by area under the curve (AUC) arterialized plasma radioactivity from beginning of the scan to the end(30).

$$Renal\ Clearance_{FDG} = {}^{FDG_{urine}}\Big/_{AUC_{0\rightarrow sampling\ time}}$$

170

171 **Rate of disappearance of [^{18}F]FDG**

172 The effect of secretin on whole-body glucose metabolism was studied using the rate
173 of disappearance (Rd) of glucose under placebo and secretin infusion. Rd is
174 calculated as follows:

175 $Rd_{glucose} = {}^{FDG_{dose} - FDG_{urine}}\Big/_{AUC_{0\rightarrow sampling\ time}} \times glucose_{0\rightarrow end\ of\ sampling}$, where

176 FDG_{dose} is the injected [^{18}F]FDG dose, FDG_{urine} is the decay-corrected quantity of
177 [^{18}F]FDG measured in the total volume of urine from [^{18}F]FDG injection to the end of
178 the PET scan, AUC is the area under the curve of [^{18}F]FDG in plasma from ^{18}F-FDG
179 injection to the end of sampling, and glucose is the average glycemia from [^{18}F]FDG
180 injection to the end of sampling (25, 43).

181

182 **Statistical analysis**

183 Sample size calculations for the primary endpoint have been previously reported(32).
184 Data are reported as means ± standard deviation (SD). Statistical analysis was
185 performed with IBM SPSS Statistics (version 27). The prespecified primary and
186 secondary endpoints of the GUTBAT Trial have been reported previously and results
187 reported here are exploratory(32). Myocardial glucose uptake is expressed as
188 µmol/100g/min. Whole body carbohydrate oxidation by indirect calorimetry is
189 expressed in kcal/d. Student's paired T-test was used to compare PET/CT data.
190 Correlation was analyzed with Pearson's correlation, unless otherwise stated. For
191 serum creatinine analysis, R-studio was used for repeated measures ANOVA. P
192 values of <0.05 were considered as statistically significant. Randomized allocation

sequences for the order of placebo and secretin interventions were generated with the randomized blocks method, with block size of 6, using SAS (v. 9.4 for Windows). The allocation sequence was generated by the Turku University statistics department, that was not otherwise involved in the study. Participants were assigned to the sequence in order of enrollment, by study personnel enrolling participants into the study.

Results

Myocardial glucose uptake (GU) was significantly higher after secretin compared to placebo (15.5 ± 7.4 vs. 9.7 ± 4.9 µmol/100g/min, p=0.004) (**Figure 2 A+B**). Secretin induced myocardial GU was not associated with previously reported insulin levels(32) (Spearman correlation between myocardial GU and plasma insulin at 0 min r=0.527, p=0.123; 20 min r=0.275, p=0.441; 60 min r=0.092, p=0.800; 120 min r=0.080, p=0.827). Previously reported serum insulin, glucose and free fatty acid levels are shown in **Supplemental Table S1** (https://doi.org/10.6084/m9.figshare.16912816 https://figshare.com/s/17330d39e276677da6bc) (32). There was no significant difference in heart rate between the interventions at one hour (57 ± 8 beats per minute (bpm) vs. 57 ± 8 bpm, p=0.92), which suggests that secretin does not have a chronotropic effect. This is supported by previous studies(21, 22). Interestingly, QTc was shortened after the two secretin infusions at one hour compared to placebo (410.2 ± 26.1 ms vs. 417.0 ± 21.7 ms, p=0.045). All ECG interval results are shown in **Table 1**.

In order to further investigate whether the increase in glucose uptake is due to increased heart work, we analyzed associations between myocardial GU and previously reported whole body energy expenditure. Whole body energy expenditure, which was 2 % higher after secretin compared to placebo(32), was not associated with myocardial GU (r=-0.07, p=0.79). This could indicate that the catabolic effect of secretin is not driven by heart work. However, whole body carbohydrate oxidation (CHO) was strongly associated with myocardial GU (r=0.555, p=0.032), which could indicate that glucose taken up by the myocardium is oxidized (**Fig. 2C**).

Rate of disappearance of glucose (Rd) was significantly higher after secretin compared to placebo (11.9 ± 2.2 vs. 10.8 ± 1.6 µmol/Kg/min, p=0.045), which is indicative of increased whole-body GU during secretin infusion. We reported in our previous study, that brown adipose tissue (BAT) and skeletal muscle glucose uptake are increased by secretin compared to placebo(32). Skeletal muscle has the largest influence on whole body glucose metabolism, due to its large mass compared to BAT and the myocardium (**Supplemental Table S2** (https://doi.org/10.6084/m9.figshare.16912810 https://figshare.com/s/5264f83bc382388e2e56)). Interestingly, glucose uptake of BAT is associated with myocardial GU after the secretin infusion (r=0.592, p=0.020), while muscle GU is not (r=0.270, p=0.331) (**Fig. 3A+C**). This could indicate that both myocardial and brown adipose tissue glucose uptakes are increased by the direct effect of secretin through secretin receptors(33), while the effect is not as pronounced in skeletal muscle. In contrast, muscle GU and myocardial GU are

associated in fasting conditions (**Fig. 3D**), while BAT GU and myocardial GU are not (**Fig. 3B**). Fatty acids are utilized as an energy source in fasting conditions instead of glucose and BAT is largely inactive.

Serum creatinine was measured as part of a metabolomics panel, taken at several timepoints during the scan (**Fig. 1**). Serum creatinine levels decreased from baseline after secretin, while no such decrease was observed subsequent to placebo administration (**Fig. 4A**). Accordingly, eGFR was increased from baseline after secretin at thirty minutes, compared to placebo (**Fig. 4B**). This is also when serum secretin levels peaked, as reported by us previously(32). [^{18}F]FDG renal clearance was significantly higher after secretin compared to placebo (secretin vs. placebo, 44.5 $\pm$ 5.4 ml/min vs. 39.5 $\pm$ 8.5 ml/min, p=0.004) (**Fig. 4C**). Urine volumes at the end of the study were not significantly different between interventions (secretin vs. placebo, 380.9 $\pm$ 138.1 vs. 338.1 $\pm$ 199.5, p=0.391).

Discussion

The main findings of this study are that secretin induces an increase in myocardial glucose uptake and increases renal filtration, as indicated by the increased eGFR and clearance of [^{18}F]FDG. Cardiac mortality benefits, shown by GLP-1 agonists, have sparked an interest in the cardiac effects of GI peptides, but the effects of secretin have not been previously studied in humans with modern imaging methods. Furthermore, the renal effects of any potential cardiovascular medications are of particular interest since renal failure exacerbates heart failure and *vice versa*. Our results in healthy, normal weight males indicate that further studies on secretin in reno-cardiovascular pathologies are warranted.

Secretin is a prandial hormone, secreted by S-cells in the duodenal epithelium. Its secretion is stimulated by the acidification of the duodenal lumen upon gastric emptying(28) and it binds to the G protein-coupled human secretin receptor(18). Secretin has an important role in the initiation of digestion, as it stimulates pancreatic exocrine secretion(28). Recently we showed that it also has a role in postprandial thermogenesis and the termination of feeding through a gut – BAT – brain axis(33). Since cardiac output also increases postprandially(58), possibly to supply the splanchnic vasculature and facilitate nutrient distribution and digestion, we propose that secretin has a role in inducing this increase.

The cardiovascular effects of secretin were studied already thirty years ago, but possibly due to enalapril showing mortality benefits in heart failure and thus catching focus(14), and the practical pharmacological challenges of secretin being an

intravenous drug with a short half-life(31), the potential of secretin as a treatment for heart failure was not further pursued. In the studies conducted by Gunnes et al, measurements were made with pulmonary artery catheterization and thermodilution technique, while ECG and femoral artery pressure were also monitored(21, 22). Secretin induced an increase in cardiac output and a drop in systemic resistance. A reduction in systemic resistance increases output, but since the increase was considerable (~20 percent), the authors suggested an inotropic effect as well. Animal studies have further confirmed this. In rat cardiomyocytes, secretin receptors stimulated contraction due to accumulation of cyclic adenosine monophosphate (cAMP) in cells(7). In pigs, intracoronary secretin increased cardiac function and perfusion through nitric oxide release and β-adrenoceptors(20). In coronary endothelial cells, this was also mediated through cAMP signaling and the effects were abolished by a secretin receptor agonist(20). cAMP production is induced by G_s coupled secretin receptor activation(18). Interestingly, G_q coupling of the receptor is also recognized and it induces intracellular calcium mobilization(18). This could also contribute to increased cardiomyocyte contraction, but to our knowledge, the mechanism has never been investigated.

In addition to the shown increase in cardiac output(21, 22), one study also showed that secretin levels are associated with normal cardiac function. Circulating gastric peptide levels were measured in patients with chronic heart failure(38). Out of the gastric peptides studied, secretin and gastrin-releasing peptide were significantly lower in patients with chronic heart failure, compared to controls(38). This was not the case with vasoactive intestinal peptide (VIP), gastric inhibitory peptide (GIP), insulin or glucagon(38). This could indicate a disturbance of secretin secretion in

chronic heart failure patients. One possible explanation could be the sympathetic activation and increase in B-type natriuretic peptide (BNP) levels in heart failure patients, which lead to increased white adipose tissue lipolysis(29). Since secretin is a powerful lipolytic agent(46), it could be downregulated between meals due to increased circulating FAs. There have not been studies addressing this question.

The heart is an omnivore, utilizing glucose, FAs, lactate and ketones for its metabolism, but long chain fatty-acids are the main substrate for energy metabolism(16). The rate of cardiac FA uptake is mostly determined by arterial FA concentration(1), whereas glucose uptake is regulated mainly through the recruitment of insulin sensitive GLUT4 transporters(34). Glucose becomes the main substrate postprandially, when glucose and insulin levels are high(48). It is notable, that secretin increased myocardial glucose uptake in our study, despite the concomitant increase in circulating FAs(32). Infusing FAs during a hyper insulinemic euglycemic clamp is known to decrease myocardial glucose uptake in humans(39), confirming *in vivo* the Randle cycle. Furthermore, fasting myocardial [^{18}F]FDG uptake has shown to correlate with increased heart work(17, 35). Taken together, our results support an inotropic effect of secretin, which was suggested in previous studies that showed an increase in cardiac output and stroke volume(21, 22).

Another interesting finding of this study was, that QTc was shortened after secretin compared to placebo, while there was no difference in heart rate. QTc interval shortens postprandially(51) and previous studies indicate that the change is not associated with insulin or glucose levels(50). In contrast, high carbohydrate uptake and high insulin levels have been tied to a postprandial increase in heart rate(45). It

has been suggested, that postprandial QTc shortening is associated with the signaling pathways of Ca^{2+} cycling(49). This would be in line with a known postprandial increase in inotropy, also involving Ca^{2+} cycling(49). Taken together, our results suggest that secretin could influence postprandial QTc shortening through inotropy. This warrants further studies.

SGLT2 inhibitors have sparked a new interest in the cardiorenal axis, as the drug class has shown benefits in both kidney and cardiovascular endpoints(55). Renal and heart failure exacerbate each other, and prescribed medications should ideally aim to treat both conditions simultaneously. In line with previous studies that have shown a diuretic effect of secretin(2, 42), our study also suggests a mild diuretic effect of secretin, as shown by the enhanced [^{18}F]FDG renal clearance. [^{18}F]FDG is filtrated into the urine, and in contrast to glucose, it is not reabsorbed by SGLT2(40). Thus, it could reflect urine excretion. It is also of note, that the increase in [^{18}F]FDG clearance occurred despite higher myocardial GU during the secretin experiment. This suggests that our [^{18}F]FDG clearance and glucose uptake results are, if any, under rather than overestimated.

Glomerular filtration rate was estimated using serum creatinine levels according to the Cockroft-Gault equation(13). eGFR values are dependent not only on the rate of creatinine filtration, but also on the rate of creatinine production by the muscle. It is thus possible, that the results reflect a decrease in creatinine production. However, there is no previous literature to support this in relation to secretin and our [^{18}F]FDG renal clearance rate results support an increase in glomerular filtration. Interestingly, creatinine clearance rate has previously been shown to associate with brown

adipose tissue activation in humans(19). The authors proposed that this could reflect an increase in creatine phosphate turnover, as eGFR also increases after muscular exercise(44). Beige adipose tissue thermogenesis is enhanced by a creatine-driven substrate cycle(26), one that has also been shown to have a role in diet induced thermogenesis in mice(27). The study showed that the genetic depletion of adipose creatine metabolism drives diet induced obesity(27). Since we previously showed that secretin activates brown adipose tissue(33), the increase in eGFR could also reflect BAT activation. Furthermore, brown adipose tissue glucose uptake was associated with myocardial glucose uptake after secretin, which indicates that the effects are linked. This is an interesting finding, since brown adipose tissue activity has recently been shown to associate with cardiovascular health, especially in obese patients(6).

Strengths of the present study are the use of state-of-the art techniques to measure myocardial substrate uptake rates *in vivo*, and the randomized placebo-controlled crossover protocol used. Our study also has limitations. First, the sample size, even though sufficient for the primary endpoints of this clinical trial, was relatively small. Infusion volumes of saline were not controlled since urine volume was not a prespecified endpoint in this study. These factors may have precluded us from finding a significant change in urine volume excretion induced by secretin. Our subjects were all healthy males and further studies are needed in order to determine whether our results are applicable to a wider population.

In conclusion, our study supports the previous hypothesis that secretin has an inotropic effect in humans. This is the first study to demonstrate that secretin may

directly impact myocardial glucose metabolism, despite concomitant increase in circulating FA levels. We also showed for the first time, that secretin induces QTc shortening, which is known to occur postprandially. Our results also indicate that secretin increases renal filtration in humans, suggesting that the hormone has an influence on the cardiorenal axis. Based on the present findings, we believe that larger studies are warranted in order to investigate whether secretin may have a place in the future treatment of heart failure.

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Author's contributions

P.N., S.L., K.V., L.N., M.K. and K.S. conceived and designed the study. S.L., M.L. and L.S. conducted the experiments. S.L., E.R., M.H., T-M.P., M.U-D. and R.K. analyzed the data. O.E. and A.K. contributed to PET/CT data collection. S.L. wrote the manuscript with input from E.R. All authors read and approved the manuscript.

Disclosures

M.K. is an inventor on a patent application from the Technical University of Munich (publication no. WO/2017/20285; international application no. PCT/EP2017/062420)

addressing the role of secretin receptor agonists and modulators in the regulation of energy homeostasis. This patent is based on the initial discovery that meal-induced secretin inhibits food intake, and this anorexigenic action of secretin depends on the activation of brown fat(33). The remaining authors declare no competing interests.

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Figure 1. Overview of the scanning protocol.

Two PET/CT scans were conducted in fasting conditions, in a single-blinded and randomized order, with a placebo (saline) and secretin (secretin pentahydrochloride 1 IU/kg *2) intervention. Arrows indicate the timing of intravenous secretin/placebo infusions. 150 MBq of [^{18}F]FDG was injected at 20 minutes, after which PET scanning of the neck, and then the thoracic region, was initiated. Indirect calorimetry was conducted for two hours. Timing of arterialized samples is indicated with test tube figures. 12- lead ECG was collected at timepoints 0, 60 and 120 min.

Figure 2. Myocardial glucose uptake results.

(**A**) Representative [^{18}F]FDG PET/CT vertical long axis images showing Ki of the heart after secretin and placebo infusions. Short axis images are shown in **Supplemental Figure S1** (https://doi.org/10.6084/m9.figshare.16912807 https://figshare.com/s/000c2b7c65015bcac357). (**B**) The effect of secretin infusion on myocardial glucose uptake compared to placebo (n=15). Data were analysed by Student's paired T-test. (**C**) Whole body carbohydrate oxidation (CHO) correlates with myocardial glucose uptake (MGU) after secretin administration. Data were analyzed by Pearson correlation. A line has been drawn on the data in order to indicate a significant association, while dotted curves represent confidence interval.

Table 1. ECG Intervals.

ECG intervals of n=15 subjects during secretin and placebo scans, measured before infusions, and 60 and 120 minutes after the first infusion. Data were analyzed by Student's paired T-test for each timepoint. Values are mean ± SD. ECG tracings of

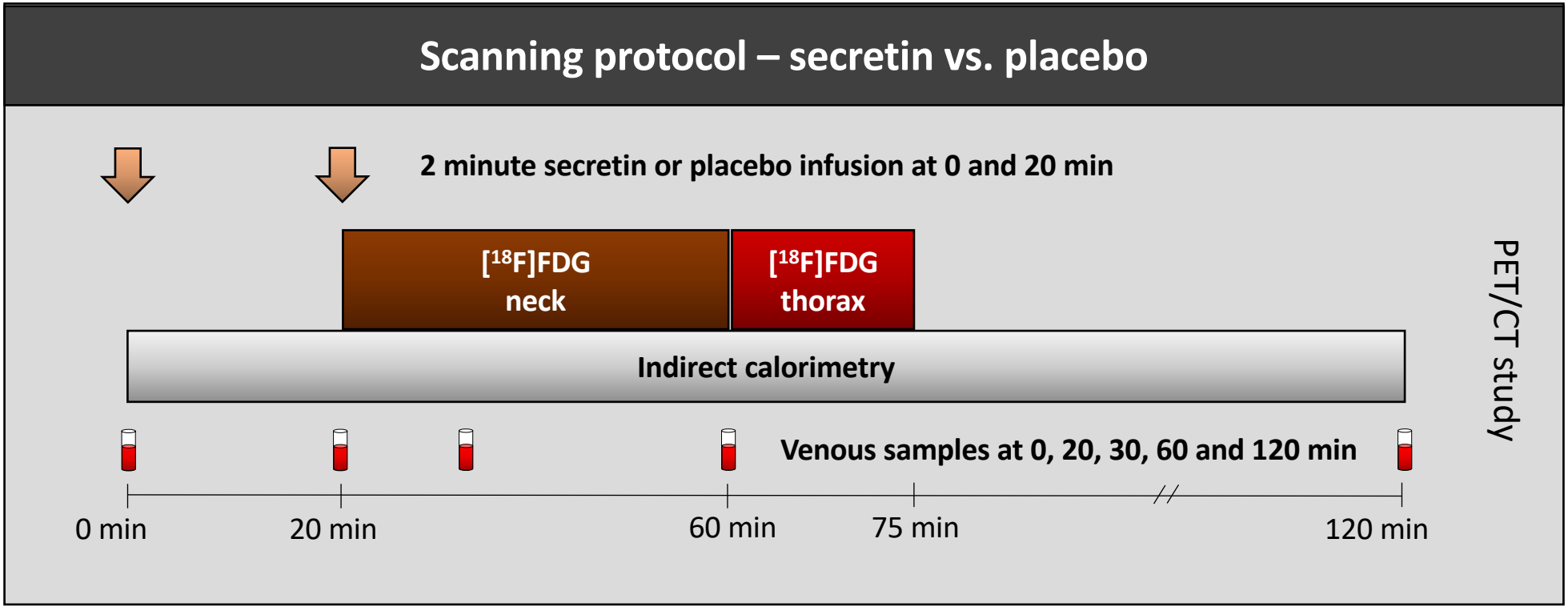
n=1 subject are shown in **Supplemental Figure S2** (https://doi.org/10.6084/m9.figshare.16912813 https://figshare.com/s/a1169ecf3785520332a3).

Figure 3. Organ glucose uptake correlations.

(**A**) Brown adipose tissue glucose uptake is strongly associated with myocardial glucose uptake after secretin infusion, (**B**) while no association is seen during placebo. (**C**) Skeletal muscle glucose uptake is not associated with myocardial glucose uptake after secretin infusion, (**D**) while an association exists during placebo. Data were analyzed by Pearson correlation. A line has been drawn on the data in order to indicate a significant association, while dotted curves represent confidence interval. All units are µmol/100g/min.

Figure 4. Renal function results.

A: Secretin decreases serum creatinine compared to placebo. Values were normalized, dividing by the value of the first time point. Mean values and standard error are shown on graph. Each timepoint was analyzed by paired Wilcoxon signed-rank test. The secretin intervention is shown in orange, while the placebo intervention is shown in grey. B: eGFR, calculated by Cockroft-Gault equation, was increased by secretin from baseline at 30 minutes, compared to placebo. C: [^{18}F]FDG renal clearance was increased after secretin. B+C Data were analyzed by Student's paired T-test.



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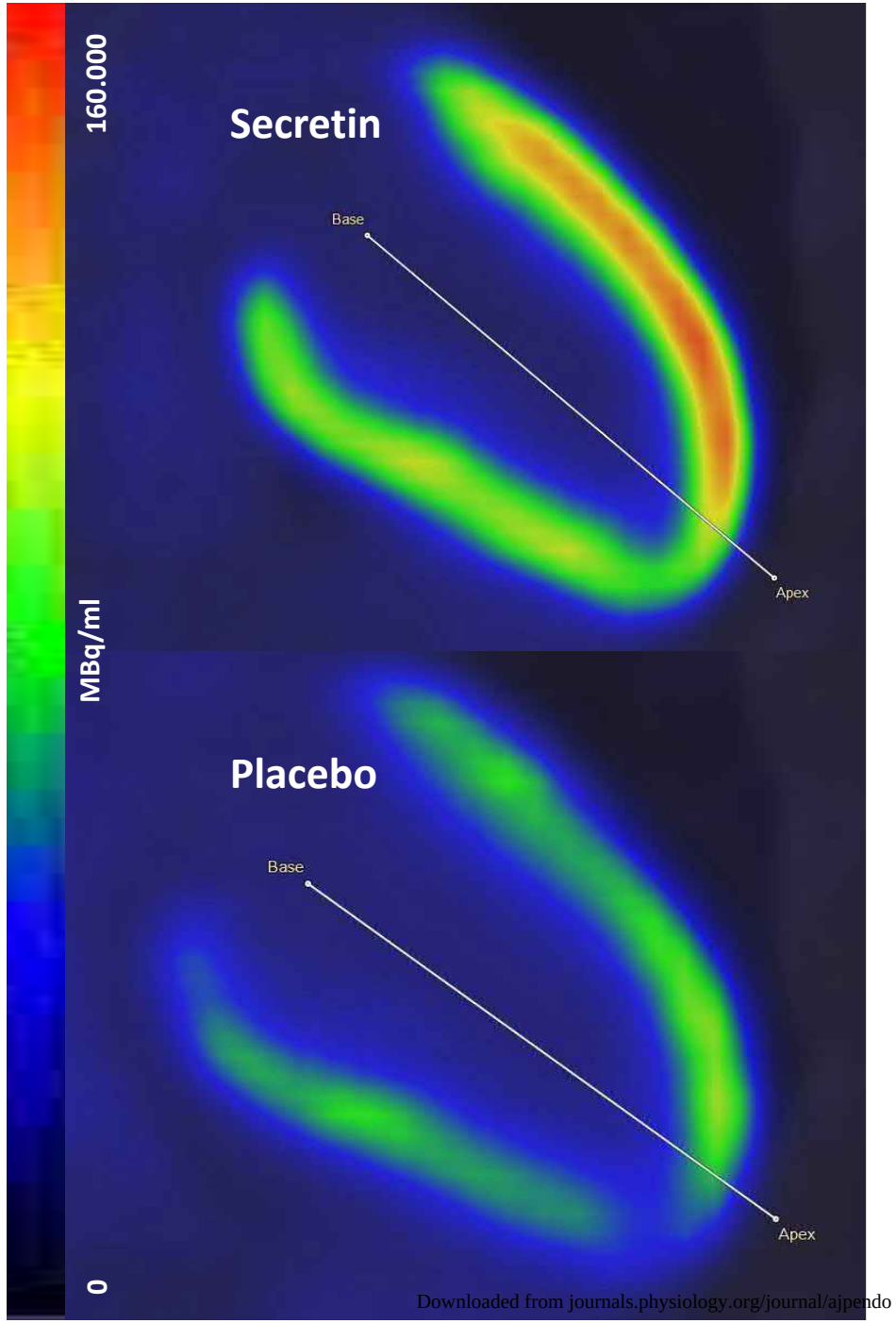

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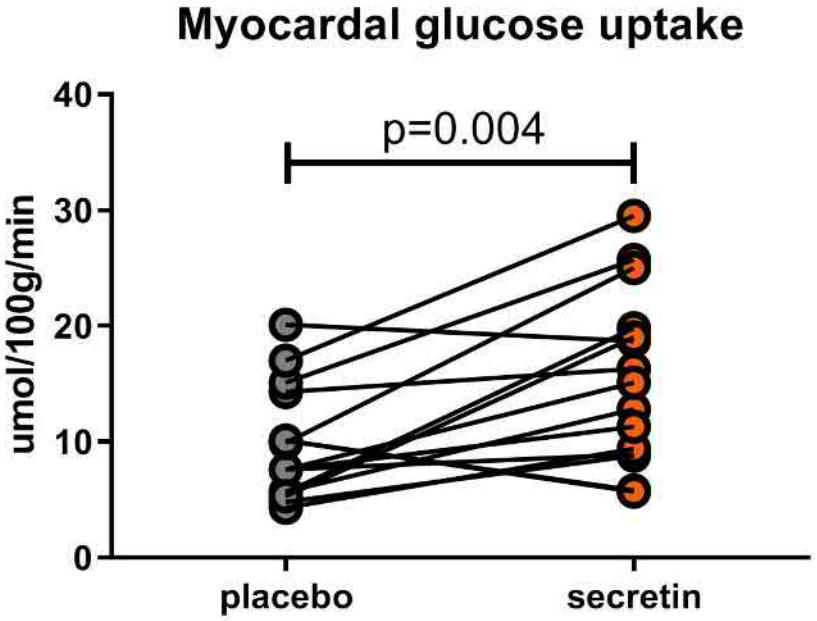

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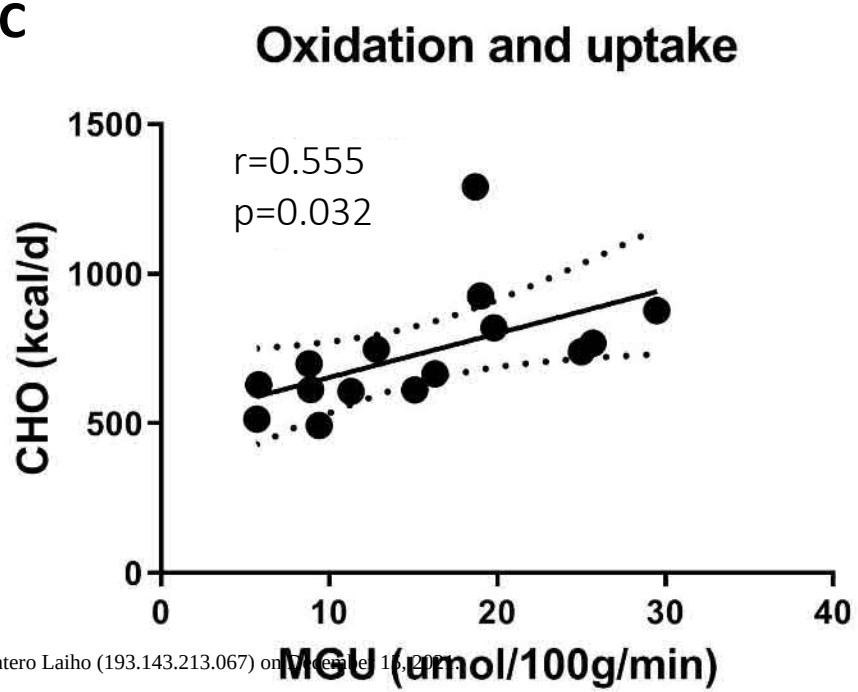
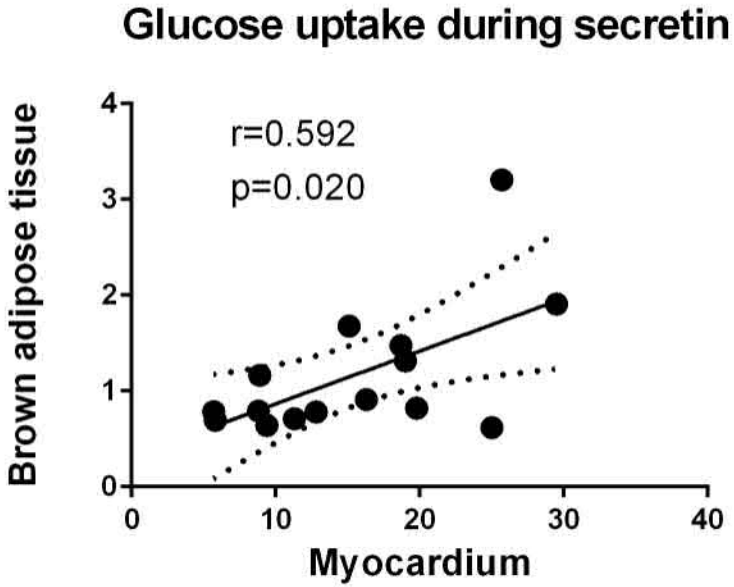


Measure	Minutes	Secretin Mean ± SD	Placebo Mean ± SD	p-value
Beats per minute (bpm)	**0**	56.6 ± 7.5	55.4 ± 8.3	0.474
	60	56.8 ± 8.0	57.0 ± 7.8	0.917
	120	59.5 ± 7.8	57.8 ± 5.4	0.313
PR (mm)	**0**	162.6 ± 24.5	158.8 ± 26.3	0.257
	60	157.4 ± 28.5	155.5 ± 24.7	0.584
	120	158.5 ± 24.7	156.8 ± 23.7	0.6
QRS (mm)	**0**	100.5 ± 10.9	100.5 ± 10.1	1.0
	60	99.8 ± 6.6	99.8 ± 8.8	1.0
	120	100.9 ± 8.0	101.5 ± 8.5	0.524
QT (mm)	**0**	428.0 ± 18.4	428.6 ± 18.0	0.899
	60	422.8 ± 13.2	429.5 ± 18.0	0.147
	120	421.9 ± 15.7	427.5 ± 13.9	0.122
QTc (mm)	**0**	414.4 ± 24.1	410.2 ± 26.3	0.485
	60	410.2 ± 26.1	417.0 ± 21.7	0.045
	120	418.9 ± 24.6	418.9 ± 19.3	0.990

A



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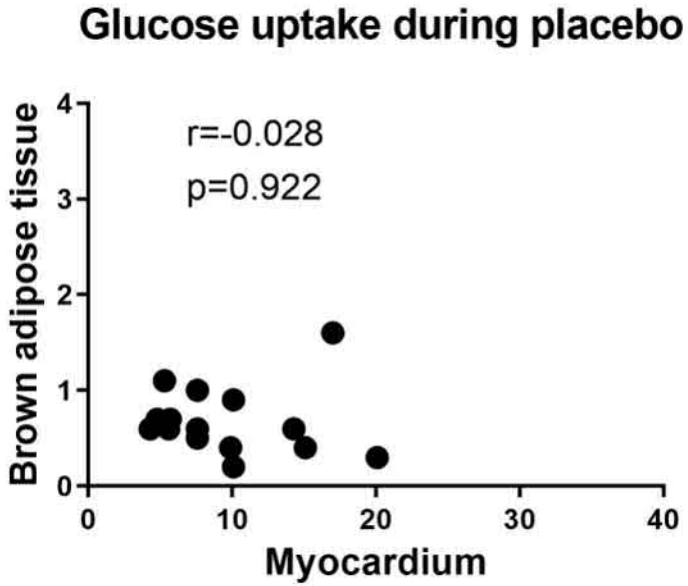

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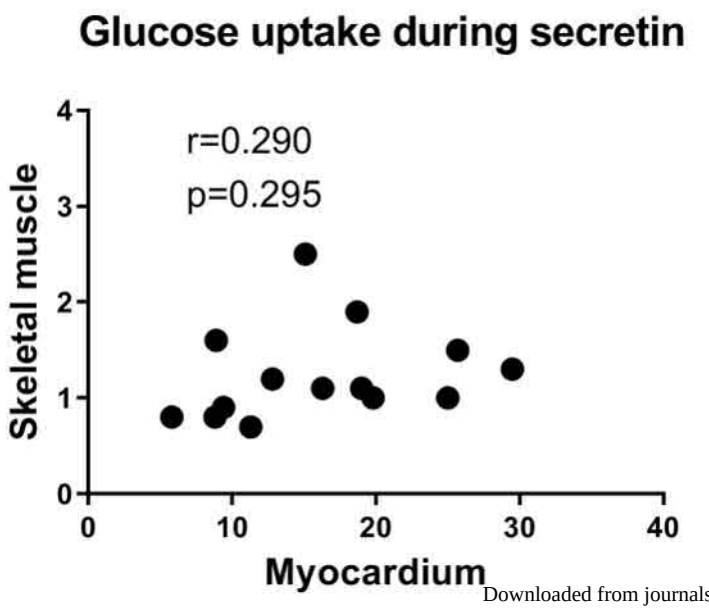

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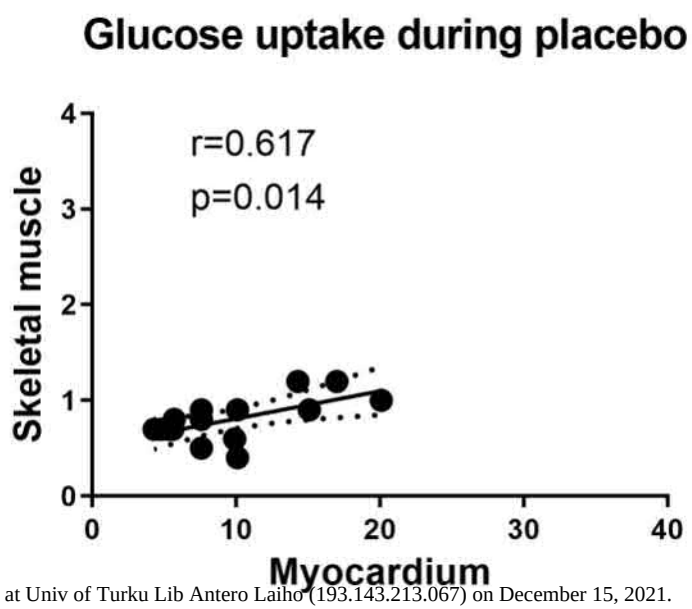
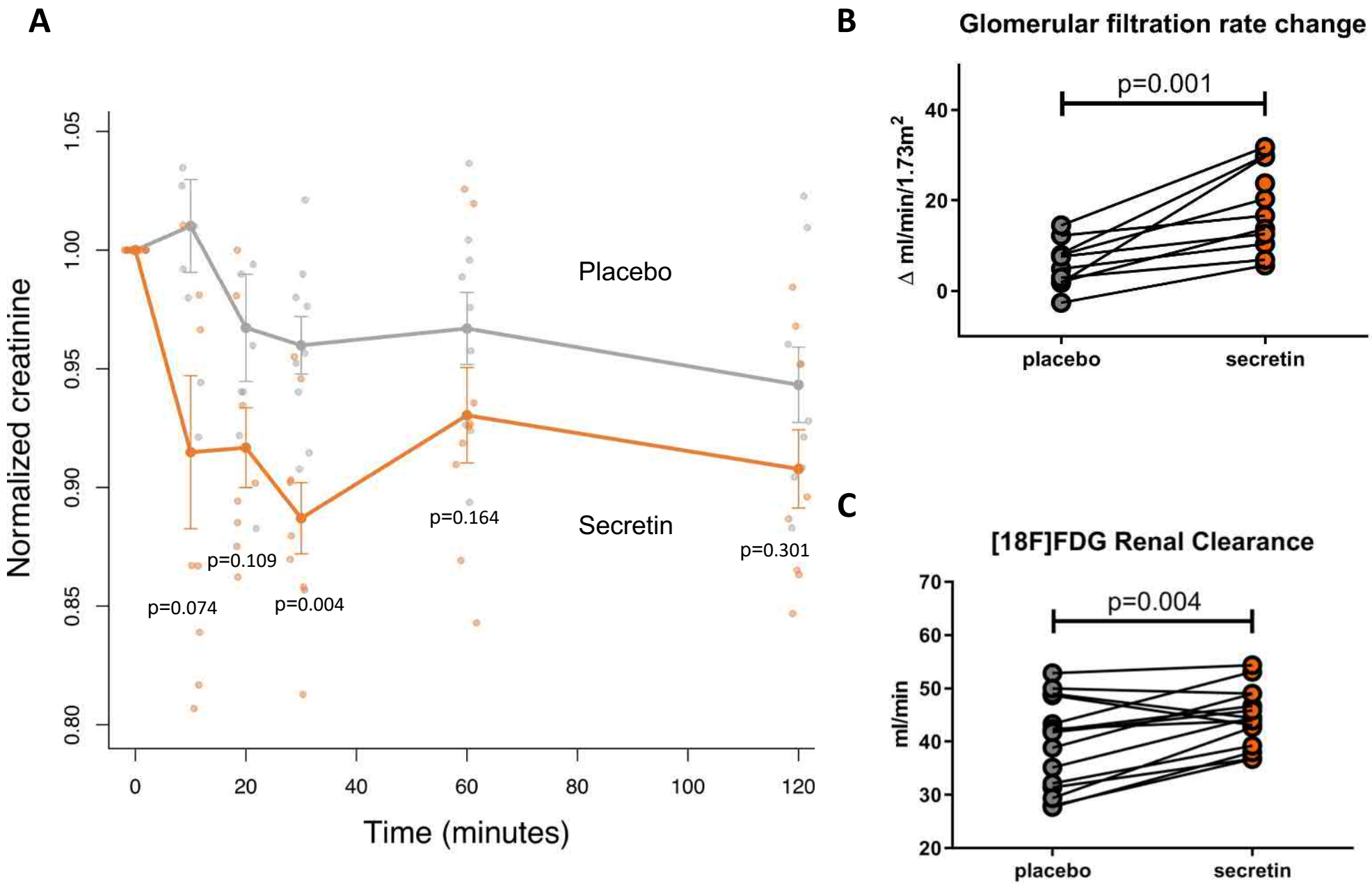
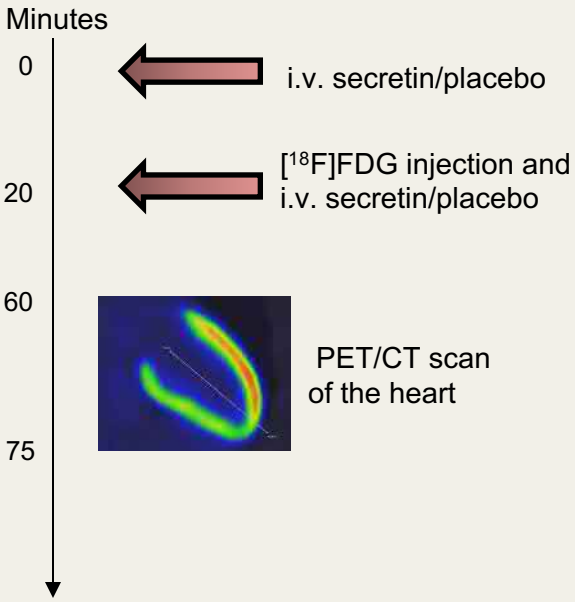




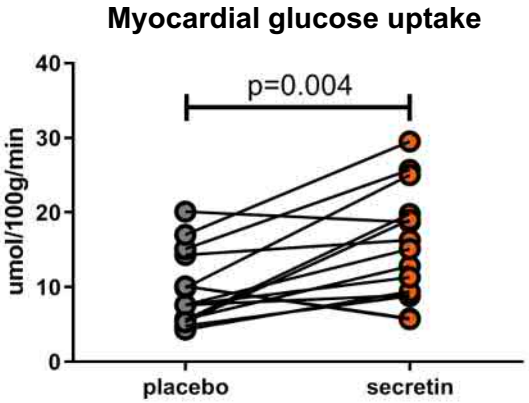
Cardiorenal Effects of Secretin

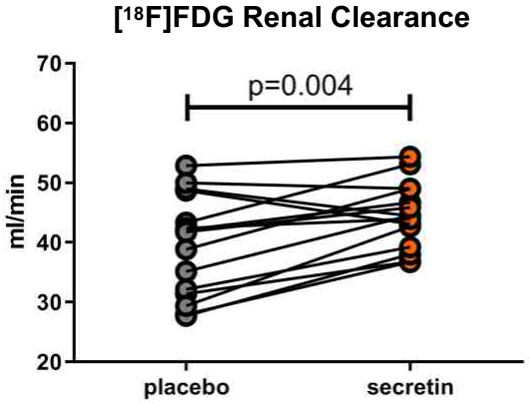
METHODS

[^{18}F]FDG PET/CT
N=15 healthy males



OUTCOME





CONCLUSION Secretin increases myocardial glucose uptake and renal clearance, making it an interesting candidate for future heart and kidney failure studies.