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Effect of Sacubitril/Valsartan on Exercise-Induced Lipid Metabolism in Patients With Obesity and Hypertension

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Abstract—Sacubitril/valsartan (LCZ696), a novel angiotensin receptor-neprilysin inhibitor, was recently approved for the treatment of heart failure with reduced ejection fraction. Neprilysin degrades several peptides that modulate lipid metabolism, including natriuretic peptides. In this study, we investigated the effects of 8 weeks' treatment with sacubitril/valsartan on whole-body and adipose tissue lipolysis and lipid oxidation during defined physical exercise compared with the metabolically neutral comparator amlodipine. This was a multicenter, randomized, double-blind, active-controlled, parallel-group study enrolling subjects with abdominal obesity and moderate hypertension (mean sitting systolic blood pressure ≥130–180 mm Hg). Lipolysis during rest and exercise was assessed by microdialysis and [1,1,2,3,3-^{2}H]-glycerol tracer kinetics. Energy expenditure and substrate oxidation were measured simultaneously using indirect calorimetry. Plasma nonesterified fatty acids, glycerol, insulin, glucose, adrenaline and noradrenaline concentrations, blood pressure, and heart rate were also determined. Exercise elevated plasma glycerol, free fatty acids, and interstitial glycerol concentrations and increased the rate of glycerol appearance. However, exercise-induced stimulation of lipolysis was not augmented on sacubitril/valsartan treatment compared with amlodipine treatment. Furthermore, sacubitril/valsartan did not alter energy expenditure and substrate oxidation during exercise compared with amlodipine treatment. In conclusion, sacubitril/valsartan treatment for 8 weeks did not elicit clinically relevant changes in exercise-induced lipolysis or substrate oxidation in obese patients with hypertension, implying that its beneficial cardiovascular effects cannot be explained by changes in lipid metabolism during exercise.

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Fatty acids are stored in the form of triglycerides in the adipose tissue and are released during lipolysis to fuel lipid oxidation in energy consuming tissues. Lipolysis and skeletal muscle lipid oxidation decrease after carbohydrate ingestion and increase in the fasting state or during physical exercise.[1] An imbalance between fatty acid mobilization and utilization may adversely affect cardiovascular and metabolic health. Acute experimental increases in circulating fatty acids in humans worsened hepatic[2] and skeletal muscle[3] insulin sensitivity and endothelium-mediated vasodilation.[4] Chronic increase in fatty acid availability promotes hepatic, skeletal muscle, myocardial lipotoxicity, dyslipidemia, insulin resistance, and type 2 diabetes mellitus.[5,6] Conversely, interventions that reduce fatty acid levels improve metabolic health.[5] These observations are highly relevant for cardiovascular medications with the potential to affect lipid turnover.

Sacubitril/valsartan, comprising a novel neprilysin inhibitor prodrug sacubitril and angiotensin receptor blocker (valsartan), has been approved for the treatment of chronic heart failure (HF; NYHA [New York Heart Association] Class II-IV) with reduced ejection fraction.[7] The endopeptidase neprilysin is ubiquitously expressed, including in human adipocytes, and degrades multiple peptides such as natriuretic peptides (NPs), angiotensin II, bradykinin, and endothelin that may modulate lipid metabolism.[8,9] Notably, NPs potently augment human adipose tissue lipolysis, postprandial lipid oxidation, and skeletal muscle oxidative capacity,[9] whereas angiotensin II elicits more subtle changes in fatty acid turnover.[10] Given the role and association

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of aberrant NP- and renin-angiotensin-aldosterone signaling in cardiovascular diseases and metabolic dysfunction, we hypothesized that simultaneous blockade of angiotensin receptor and neprilysin with sacubitril/valsartan can potentially ameliorate metabolic dysfunction, especially lipid turnover, compared with amlodipine. In the present study, we investigated the effects of 8-week treatment with sacubitril/valsartan compared with the metabolically neutral comparator amlodipine on whole-body and adipose tissue lipolysis, energy expenditure and substrate oxidation during defined physical exercise, which is known to stimulate NP release and induce lipolysis and lipid oxidation.

Methods

Study Design

The study design, key inclusion and exclusion criteria of the patients, and the primary results of this study have been described earlier.[11] Briefly, this was a multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-group study enrolling adult subjects with abdominal obesity (waist circumference ≥102 cm for men and ≥88 cm for women) and moderate hypertension (mean sitting systolic blood pressure [BP] ≥130 and <180 mm Hg). Key exclusion criteria were severe hypertension (mean sitting systolic blood pressure ≥180 mm Hg), type 1 or 2 diabetes mellitus (fasting plasma glucose ≥126 mg/dL or HbA1c ≥6.5%), dyslipidemia requiring therapy with fibrates or nicotinic acid, concomitant use of antihypertensive, antidiabetic or other medications that affect glucose or lipid metabolism, and a history or current diagnosis of HF (NYHA class II-IV).

The study included a screening period of up to 4 weeks followed by a 4-week washout period and an 8-week randomized, double-blind, and double-dummy treatment phase. Patients receiving antihypertensive medications at the time of screening discontinued the therapy during the washout period. During the treatment period, patients were randomized to receive either sacubitril/valsartan 400 mg every day (QD) or amlodipine 10 mg QD along with a matching placebo for 8 weeks. Patients were stratified into 4 groups based on baseline homeostatic model assessment of insulin resistance and statin use.

All patients provided written informed consent before screening. The clinical study protocol was reviewed and approved by the Independent Ethics Committee or Institutional Review Board at each center and, conducted in accordance with the declaration of Helsinki.

Exercise Test

An incremental exercise test on a bicycle ergometer was conducted before the start of intervention (day −14) to determine the maximal aerobic capacity (VO_2 peak) at volitional exhaustion by measuring the individual maximum workload before stopping for exhaustion or until predefined heart rate or BP criteria were met. At baseline (day 1) and after 8 weeks (day 57), subjects exercised at 50% of Vo_2 peak (as determined on day −14) for a period of 60 minutes.

Measurement of Lipolysis

Local adipose tissue and whole-body lipolysis were assessed at baseline and after 8 weeks of treatment as described previously.[11] Local adipose tissue lipolysis was measured by microdialysis and assessed during a 45-minute interval at rest, followed by a 60-minute interval during which the patients exercised at 50% of their individual Vo_2 peak. Dialysates were collected from abdominal subcutaneous adipose at the lower right abdominal quadrant at rest and at 15-minute intervals during exercise. Concentrations of glycerol (as an indicator of lipolysis), glucose, and lactic acid in dialysates were measured. The ethanol outflow/inflow ratio (ratio of ethanol concentration in the dialysate and perfusate) was measured as an indicator of adipose tissue blood flow.

Whole-body lipolysis was estimated using [1,1,2,3,3-^{2}H]-glycerol tracer kinetics after an intravenous glycerol bolus (2 μmol·kg^{-1}) after insertion of the microdialysis catheter, ≈60 minutes before the baseline measurements started, and subsequent infusion at an infusion rate of 0.1 μmol·kg^{-1}·min^{-1} at rest and 0.2 μmol·kg^{-1}·min^{-1} during exercise. Blood samples were collected at 15-minute intervals at rest and during exercise. The rate of appearance of endogenous glycerol was calculated as the ratio of glycerol tracer infusion rate:plasma glycerol tracer enrichment. At steady state, glycerol rate of appearance was calculated from glycerol enrichment using Steele equation.

Energy Expenditure and Substrate Oxidation

Energy expenditure and substrate oxidation during rest and exercise were assessed by indirect calorimetry using a ventilated hood system. The ventilated hood measurements were recorded for 30 minutes in the resting phase with the patient in supine position and during the last 10 minutes of the 60-minute exercise period.

Circulating Metabolites and Hormones

Samples for fasting plasma biomarkers (nonesterified fatty acid [NEFA], glycerol, glucose, insulin, adrenaline, and noradrenaline) were collected at baseline (day 1) and on day 57 at rest and during exercise concurrently with microdialysis measurements.

Blood Pressure

Office BP was measured at screening, during washout and throughout the study at baseline, week 4, week 8, and at the end of study using the same arm and the same automated equipment with an appropriate cuff size. Measurements were performed in triplicate at 2-minute intervals after patients had been sitting for 15 minutes with the back supported and both feet on the floor. BP was also measured during the exercise phase. During the home stay period, patients were given a home measurement device and instructed to monitor BP twice weekly at approximately the same time each morning.

Statistical Analysis

After 8 weeks of treatment with sacubitril/valsartan or amlodipine, assessments of local adipose tissue lipolysis, whole-body lipolysis, oxidative metabolism, BP, and biomarkers during exercise were performed as prespecified study objectives.

For abdominal subcutaneous adipose tissue microdialysate data (ethanol ratio, dialysate lactate, dialysate glucose, and dialysate glycerol), plasma biomarkers (glycerol, NEFA, glucose, insulin, adrenaline, and noradrenaline), and whole-body lipolysis (rate of glycerol appearance) data for 45 minutes at rest and 4 time points during exercise (15, 30, 45, and 60 minutes) were analyzed using repeated measures analysis on log-transformed values with treatment, visit, time, and treatment×visit×time interaction as fixed effects. Geometric mean ratios of each exercise time point to 45-minute resting for each day and treatment, ratios of day 57 to day 1 for each treatment and each exercise time point, and the ratio between sacubitril/valsartan and amlodipine for day 57 to day 1 were calculated.

Oxidative metabolism was analyzed using ANCOVA with treatment as the fixed effect and baseline as the covariate. Oxidative metabolism during exercise was analyzed using ANOVA for repeated measurements with treatment, visit, and treatment×visit interaction as fixed effects. Mean difference to day 1 (day 57 versus day 1) for each treatment along with the corresponding 95% confidence intervals and *P* values are presented. Data for exercise and resting phase were analyzed for each day and treatment with a mixed-effects linear model with phase (exercise or resting) as the fixed effect and subject as the random effect to obtain the mean difference estimate and 95% confidence interval for exercise versus rest comparison. Respiratory quotient (CO_2/O_2 ratio) was calculated at each of the days 1 and 57 at rest and during exercise. A statistical comparison of the quotients was then made between rest and exercise within each day.

Results

Exercise Testing

On day 1, 39 patients randomized to the sacubitril/valsartan group and 24 patients randomized to the amlodipine group completed the constant workload exercise for 60 minutes. On day 57, 36 patients treated with sacubitril/valsartan and 23

treated with amlodipine completed the exercise for 60 minutes. Similar observations were made in patients completing only 45 and 60 minutes of exercise, suggesting that 8 weeks of treatment of patients with obesity and hypertension with sacubitril/valsartan or amlodipine did not have any clinically relevant impact on the exercise duration. Oxygen consumption and workload were comparable between days 1 and 57 in both treatment groups (Table S1 in the online-only Data Supplement).

Plasma Glucose and Insulin Concentrations

With exercise, plasma glucose concentrations increased in the amlodipine group for all time points and for 30 minutes (P=0.017), 45 minutes (P=0.002), and 60 minutes (P<0.001) in the sacubitril/valsartan group on day 1. On day 57, the increase was significant during 60 minutes of exercise in the sacubitril/valsartan group (P=0.031) but the increase was not significant at any time point in the amlodipine group. A decrease in glucose levels was noticed on day 57 in both treatment groups as compared with baseline (day 1), with the difference being significant only in the amlodipine group at 30 minutes (P=0.017) and 45 minutes (P<0.001) of exercise. However, no statistically significant differences in glucose concentrations were observed between the treatment groups at any time point.

A decrease in insulin concentrations with increasing exercise duration was observed in both treatment groups. When compared with resting insulin concentrations, a significant decrease was observed at 45 minutes (P=0.015) and 60 minutes (P<0.001) on day 1 and at 45 minutes (P=0.044) on day 57 in the sacubitril/valsartan group. However, exercise-induced decreases in insulin concentrations were not statistically significant in the amlodipine group, either on day 1 or 57. After 8 weeks of treatment, compared with baseline, insulin concentrations were significantly lower in amlodipine group at all time points except 60 minutes, whereas the change was not significant at any time point in the sacubitril/valsartan group. Significant differences in insulin concentrations were observed at 30 minutes (P=0.017) and 45 minutes (P=0.027) between the treatment groups on day 57 compared with baseline.

Subcutaneous Adipose Tissue Lipolysis During Exercise

Compared with resting measurements, microdialysate glycerol concentrations increased during exercise indicating increased subcutaneous adipose tissue lipolysis in both the amlodipine and sacubitril/valsartan groups on days 1 and 57. Compared with baseline, microdialysate glycerol concentrations during exercise were numerically lower in the amlodipine group on day 57. In the sacubitril/valsartan group, microdialysate glycerol concentrations increased similarly at the beginning and at the end of treatment, but this increase was not statistically significant (Figure 1). Microdialysate glucose concentrations were comparable between sacubitril/valsartan and amlodipine at baseline (sacubitril/valsartan versus amlodipine: 15 minutes [1.07 versus 0.94 mmol/L]; 30 minutes [1.06 versus 1.02 mmol/L]; 45 minutes [1.05 versus 0.99 mmol/L]; and 60 minutes [1.03 versus 0.91 mmol/L]) and on day 57 (15 minutes [1.12 versus 0.95 mmol/L]; 30 minutes [1.08 versus 0.94 mmol/L]; 45 minutes [1.07 versus 1.02 mmol/L]; and 60 minutes [1.06 versus 1.01 mmol/L]). No statistically significant differences in glucose levels from baseline to week 8 were observed for any time points in both the treatment groups. No significant differences were observed between the two treatment groups. A similar trend was observed for lactate levels.

Ethanol ratios were comparable between sacubitril/valsartan and amlodipine on day 1 (sacubitril/valsartan versus amlodipine: 15 minutes [0.42 versus 0.43]; 30 minutes [0.42 versus 0.44]; 45 minutes [0.43 versus 0.45]; and 60 minutes [0.47 versus 0.46]). Ethanol ratios increased on day 57 in both the sacubitril/valsartan and amlodipine groups, but remained comparable between treatment groups (15 minutes [0.49 versus 0.49]; 30 minutes [0.51 versus 0.49]; 45 minutes [0.53 versus 0.51]; and 60 minutes [0.55 versus 0.53]). These data suggest that there were no relevant change in blood flow that needs to be accounted for when interpreting glycerol measurements.

Whole-Body Lipolysis

Plasma glycerol concentrations increased with exercise in both treatment groups, both on days 1 and 57 (amlodipine group, day 1 versus 57: resting [89.77 versus 88.04 μmol/L]; 15 minutes [141.12 versus 119.56 μmol/L]; 30 minutes [184.78 versus 156.03 μmol/L]; 45 minutes [216.04 versus 179.27 μmol/L]; and 60 minutes [224.85 versus 191.95 μmol/L]) and sacubitril/valsartan, day 1 versus 57: resting [85.64 versus 83.93 μmol/L]; 15 minutes [139.3 versus 126.92 μmol/L]; 30 minutes [177.65 versus 157.29 μmol/L]; 45 minutes [205.68 versus 189.84 μmol/L]; and 60 minutes [225.62 versus 205.26 μmol/L]). Compared with baseline, plasma glycerol levels were lower in both the treatment groups on day 57. Although the change from baseline to day 57 was significant at all time points in the amlodipine group (P<0.05), it was significant at 30 minutes in the sacubitril/valsartan group (P=0.012). The differences in plasma glycerol levels between treatment groups were not significant.

As compared with glycerol rate of appearance after 45-minute rest, a significant increase was observed during exercise at all time points in both treatment groups on days 1 and 57 (P<0.001). The change from baseline to day 57 was statistically significant in the sacubitril/valsartan group at 15 minutes (P=0.026), 30 minutes (P=0.012), and 45 minutes (P=0.035) but was not significant at any time point in the amlodipine group (Figure 2A). However, there was no significant difference between treatment groups at any time point.

Plasma NEFA concentrations decreased on day 57 at 15 minutes in the sacubitril/valsartan group (P=0.018) and at 15 and 30 minutes (P<0.05) in the amlodipine group. No significant differences were observed between treatment groups. When compared with NEFA levels at rest (for 45 minutes), the levels were lower during the initial phases of exercise, but increased gradually with increasing exercise duration in both treatment groups (Figure 2B).

Oxidative Metabolism During Exercise

Oxygen consumption was comparable between the sacubitril/valsartan and amlodipine groups at baseline (O_2 consumption: amlodipine, 1.31±0.45 L/min; sacubitril/valsartan, 1.40±0.41 L/min) and on day 57 (amlodipine, 1.27±0.39 L/min; sacubitril/valsartan, 1.37±0.44 L/min) and no differences were found between treatment groups.

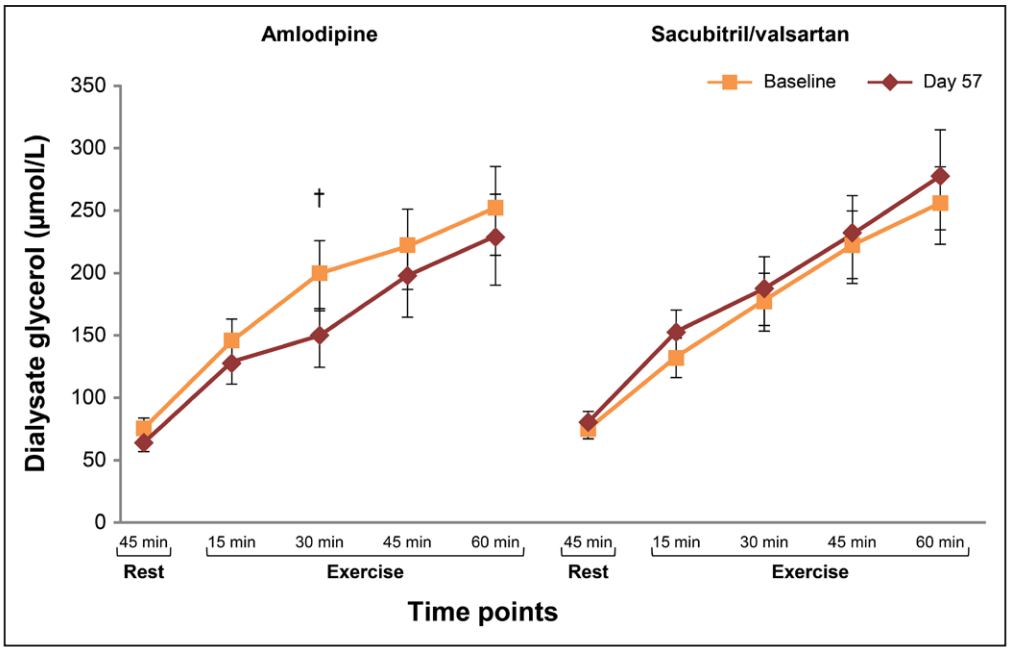

Figure 1. Comparison of local adipose tissue lipolysis (dialysate glycerol) variable during exercise following 8 weeks of treatment with sacubitril/valsartan and amlodipine. Error bars indicate 95% confidence interval. †P=0.003 vs baseline.

The respiratory quotient significantly increased during exercise in both the treatment groups, on days 1 and 57 (Figure 3). The respiratory quotient was comparable between treatments at baseline and on day 57.

Plasma Catecholamine Concentrations

When compared with resting levels, adrenaline levels increased significantly during exercise at all time points in both treatment groups on days 1 and 57 (Figure 4A). Compared with baseline, a significant reduction in adrenaline levels were observed on day 57 in the amlodipine groups at all time points, whereas the decrease was not statistically significant in the sacubitril/valsartan group. However, no significant differences were observed in the adrenaline levels between treatment groups at any time point, except at 30 minutes (P=0.012).

Plasma noradrenaline levels were significantly increased during exercise in both the treatment groups on days 1 and 57 (P<0.001) when compared with resting levels (Figure 4B). Noradrenaline levels increased incrementally during exercise on days 1 and 57 in both the treatment groups, with no significant differences between treatments.

Blood Pressure

After 8 weeks of treatment, systolic BP, diastolic BP, and pulse pressure decreased from baseline in both treatment groups at rest. Systolic and diastolic BP and pulse rate values increased during exercise in both treatment groups on both days 1 and 57 without clinically relevant differences between treatment groups (Table).

Discussion

The present study demonstrated that treatment with sacubitril/valsartan compared with amlodipine for 8 weeks did not elicit relevant changes in exercise-induced lipolysis and substrate oxidation in obese patients with hypertension. The exercise-induced increase in abdominal subcutaneous adipose tissue and whole-body lipolysis was not augmented after sacubitril/valsartan treatment compared with amlodipine treatment. Moreover, the shift in substrate oxidation toward carbohydrate catabolism during exercise was comparable in both treatment groups, implying that sacubitril/valsartan did not significantly affect lipid utilization during acute exercise. We have previously observed significantly improved whole-body insulin sensitivity and a modest increase in resting abdominal subcutaneous lipolysis, with no marked changes in whole-body lipolysis, with sacubitril/valsartan compared with amlodipine treatment.[11] Overall, these findings imply that the beneficial cardiometabolic effects of sacubitril/valsartan may not be explained by changes in lipid mobilization or oxidation.

In this study, we used state-of-the-art methodology including [1,1,2,3,3-^{2}H]-glycerol tracer kinetics and abdominal subcutaneous adipose tissue microdialysis to assess whole-body and local lipolysis, respectively, in a large patient sample. Furthermore, we treated patients with a total daily dose of sacubitril/valsartan which provided superior BP control in patients with arterial hypertension (400 mg QD)[12] and reduced cardiovascular mortality and HF hospitalizations in patients with HF and reduced ejection fraction (200 mg twice daily) compared with standard of care renin-angiotensin system inhibition.[7] This study, therefore, was appropriately designed to study the effect of sacubitril/valsartan on lipid turnover.

Our study extends previous investigations on the role of neprilysin substrates and angiotensin II type 1 (AT_1)-receptors in the regulation of lipid turnover. All components of the renin-angiotensin system are expressed in adipose tissue, and AT_1-receptors have been implicated in the regulation of adipose tissue differentiation, inflammation, and metabolism.[10] Conflicting findings have been reported with respect to the effects of angiotensin II on adipose tissue lipolysis. More specifically, both increased[13,14] and decreased[15] subcutaneous adipose tissue lipolysis have been demonstrated.[14] Moreover,

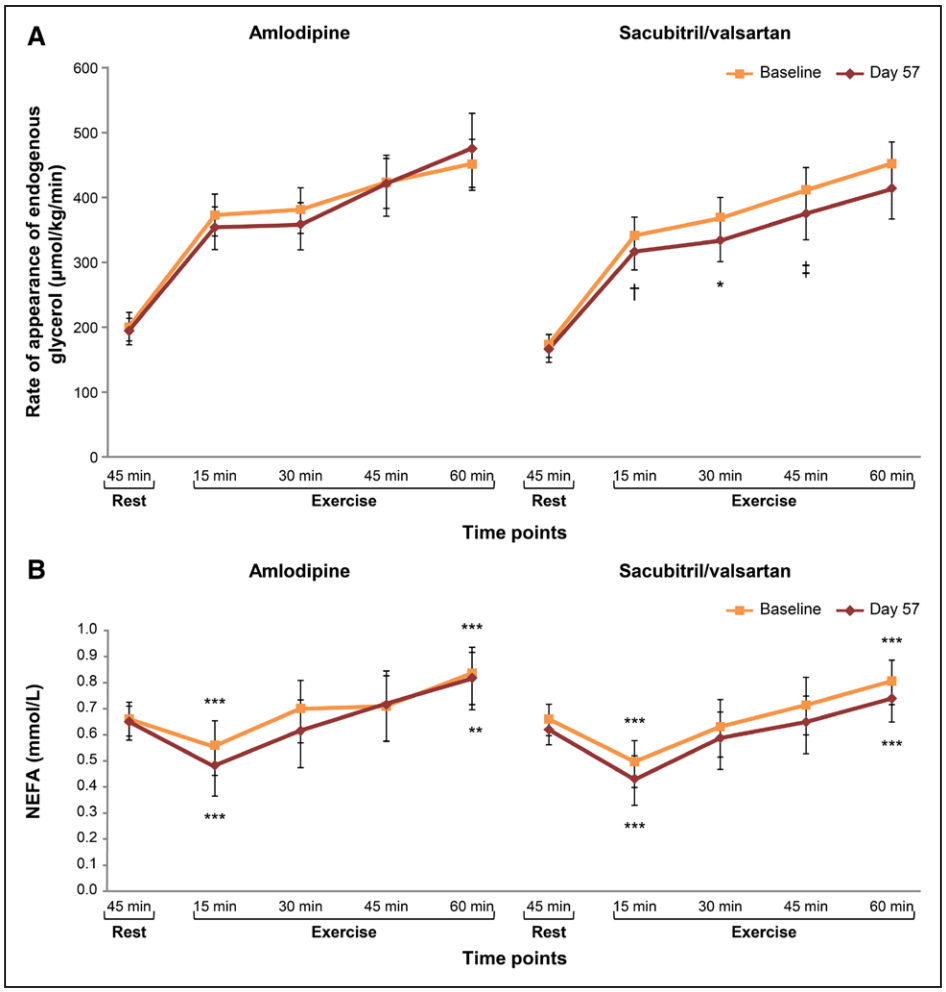

Figure 2. Whole-body lipolysis during exercise: comparison of rate of glycerol appearance between treatments (**A**) and plasma concentration of nonesterified fatty acid (NEFA; **B**). Error bars indicate 95% confidence interval. †P=0.026, *P=0.012, ‡P=0.035 vs baseline; **P=0.002, ***P<0.001 vs 45 minutes of rest.

intravenous angiotensin II infusions and angiotensin-converting enzyme inhibition did not elicit major changes in whole-body lipolysis as determined by glycerol tracer kinetics.[16] AT_1-receptor blockade in humans did not increase lipolytic gene expression or lipolysis in abdominal subcutaneous adipose tissue.[17,18] However, long-term AT_1-receptor blockade altered intramuscular lipid partitioning, manifested by decreased saturation of skeletal muscle triacylglycerol and diacylglycerol stores, reduced postprandial fatty acid spillover and lipolysis.[19] Overall, angiotensin II actions on AT_1-receptors seems to have modest effects on lipid turnover. Although postprandial fatty acid handling has not been examined in this study, the present findings suggest that AT_1-receptor blockade in the context of neprilysin inhibition by sacubitril/valsartan does not have clinically relevant effects on lipid mobilization or utilization.

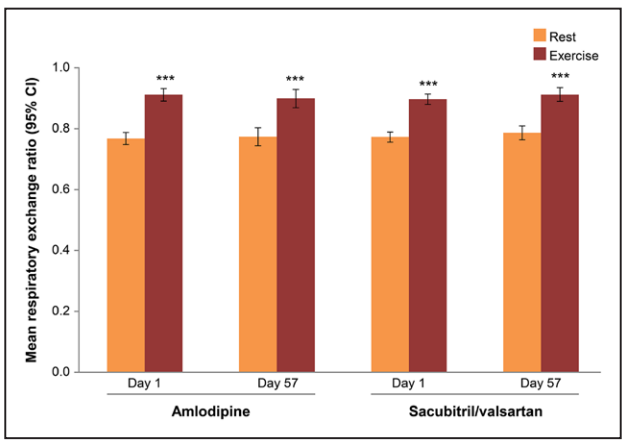

Figure 3. Oxidative metabolism: comparison of respiratory quotient between resting and exercise status, carbon dioxide:oxygen ratio. Error bars indicate 95% confidence interval. ***P<0.01, exercise versus rest.

Neprilysin degrades multiple peptides that potentially modulate lipid metabolism such as NPs, bradykinin, endothelin-1, and glucagon-like peptide 1.[20] While bradykinin has been suggested to attenuate lipolysis, endothelin-1 may increase lipolysis. However, endothelin-1 was significantly decreased after treatment of patients with HF and reduced ejection fraction with sacubitril/valsartan for 21 days, and no changes in lipolysis for glucagon-like peptide 1 at high concentrations have been reported.[21–25] As the results of this study present the net effect of sacubitril/valsartan, we cannot discern contributions of individual neprilysin substrates to the observed metabolic response nor can we rule out that opposite effects of individual neprilysin substrates result in an overall negative

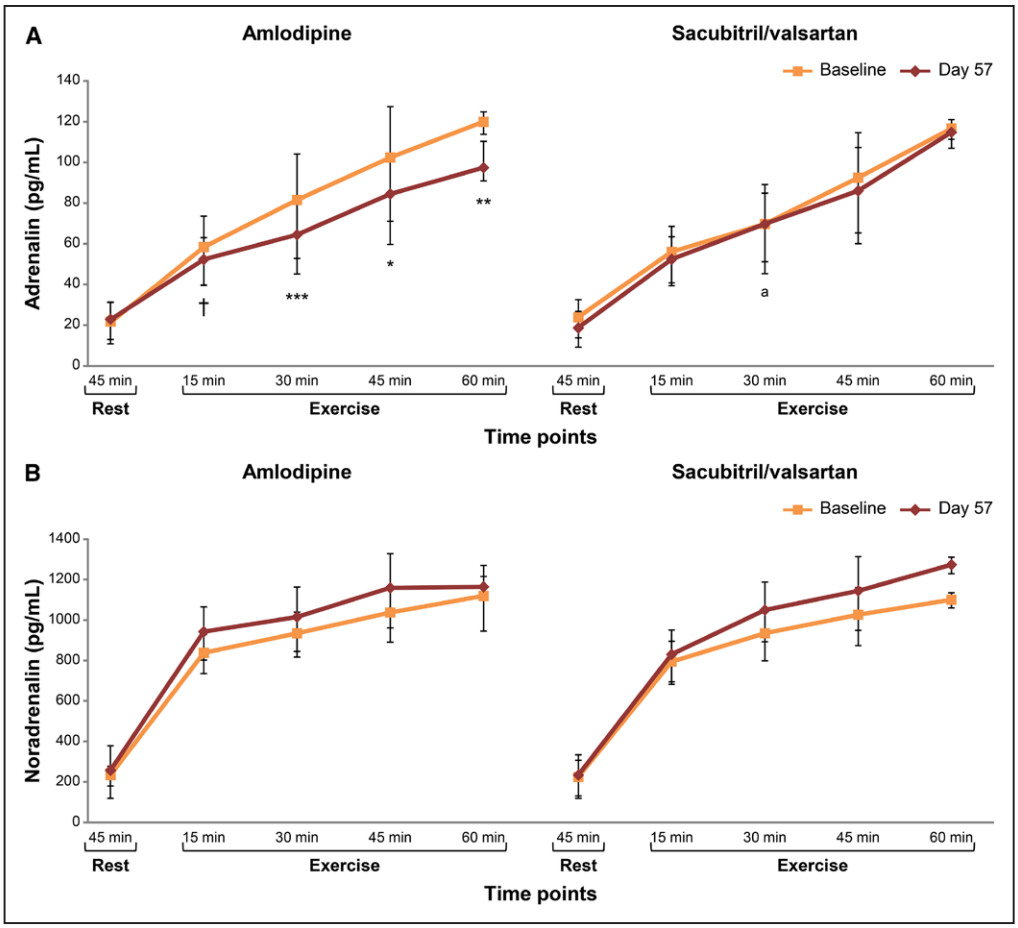

Figure 4. Analysis of plasma biomarkers during exercise: adrenaline (**A**) and noradrenaline (**B**). Error bars indicate 95% confidence interval. †P=0.044, *P=0.022, **P=0.019, ***P<0.001 vs baseline; [a]P=0.012 vs amlodipine.

effect. Among neprilysin substrates, lipolytic effects of NPs are particularly striking. In ex vivo experiments with human adipocytes, NPs were substantially more potent in stimulating lipolysis than the prototypical β-adrenoreceptor agonist isoproterenol with comparable efficacy.[26] In vivo, atrial NP infusion in physiologically relevant doses potently stimulates adipose tissue lipolysis.[27] This increase in adipose tissue lipolysis is not attenuated with systemic β-adrenoreceptor blockade.[28] Because NP-induced lipolysis is observed only in primates, the utility of many preclinical animal models is limited.[29] NPs are released during physical exercise and may provide lipid fuel to the working skeletal muscle, which is generally considered beneficial. Excess NP-mediated lipid mobilization has been suggested as a potential limitation of therapeutic neprilysin inhibition if associated with increased NEFA plasma concentrations; however, this was not observed after treatment with sacubitril/valsartan in the present study. Furthermore, the lack of changes in exercise-induced lipolysis by sacubitril/valsartan observed in the present study is clinically reassuring as ex vivo lipolysis of subcutaneous adipose tissue was not desensitized in patients with HF despite increased circulating NP levels.[30]

Given the potent acute effect of NPs on human lipolysis, our findings are somewhat unexpected. Plasma noradrenaline and adrenaline increased to a similar extent at baseline and after treatment with amlodipine and sacubitril/valsartan, suggesting that opposing changes in sympathoadrenal activity did not mask a direct treatment effect on lipolysis. The reduction in catecholamine levels observed with sacubitril/valsartan in this study is consistent with our previous observation.[11] Conflicting observations have been reported with respect to the effect of amlodipine therapy on noradrenaline levels,[31–33] whereas valsartan treatment has been demonstrated to attenuate increases in plasma noradrenaline concentrations with larger reductions from baseline associated with lower risk of mortality and morbidity.[34,35] Although sacubitril/valsartan improved insulin-mediated glucose disposal compared with amlodipine,[11] potential antilipolytic effects of insulin in adipose tissue after sacubitril/valsartan have not been investigated before. We cannot completely rule out that improved insulin action in adipose tissue confounded our analysis. However, an alternative and more likely explanation is that NP actions in adipose tissue are not, or to a lesser degree, dependent on neprilysin activity. Indeed, a study in isolated human adipocytes suggests that clearance via the NP receptor C, the so-called scavenger receptor, may be more important than neprilysin activity to control local NP availability.[36] Indeed, completely abolishing neprilysin activity using thiorphan did not modify atrial NP-mediated lipolysis.[36]

Noteworthy, we conducted our study in obese patients with hypertension. Given the differences in neurohormonal activity between patients with hypertension and HF, the extent to which our findings can be applied to patients with HF and reduced ejection fraction remains to be elucidated. However, a recent post hoc

Table. Comparison of BP and Pulse Rate Between Treatments During Exercise and Rest

BP/Pulse Rate	Day/Visit	Exercise/Rest	Sacubitril/Valsartan 400 mg QD (n=50)	Amlodipine 10 mg QD (n=48)
SBP, mm Hg	Day 1	Rest	137.9±14.67	135.8±12.82
		Exercise	157.5±23.77	146.5±23.3
	Day 57	Rest	119.9±14.28	125.9±10.23
		Exercise	146.8±21.89	137.6±20.49
DBP, mm Hg	Day 1	Resting	88.0±10.65	86.8±8.89
		Exercise	82.8±12.57	84.3±12.39
	Day 57	Resting	77.2±8.49	81.2±7.19
		Exercise	78.4±12.33	78.8±11.98
Pulse rate, bpm	Day 1	Resting	67.4±8.6	66.7±9.28
		Exercise	121.2±15.40	111.4±25.62
	Day 57	Resting	65.2±8.70	69.2±10.48
		Exercise	123.5±18.62	115.6±16.54

Data are mean±SD. BP indicates blood pressure; bpm, beats per minute; DBP, diastolic BP; QD, every day; SBP, systolic BP; and SD, standard deviation.

analysis of the PARADIGM-HF trial (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) showed that in patients with HF and type 2 diabetes mellitus, treatment with sacubitril/valsartan resulted in greater reductions in HbA1c levels compared with those treated with enalapril. Moreover, sacubitril/valsartan treated patients with type 2 diabetes mellitus were less likely to require initiation of insulin treatment during the trial suggesting potential metabolic benefits of sacubitril/valsartan therapy in HF patients.[37] Another potential limitation of the study is that we ascertained the effect of sacubitril/valsartan therapy on only exercise-induced lipolysis, which is one of the strong physiological stimuli regulating lipolysis. However, it remains to be elucidated whether the findings of our study can be extrapolated to other physiological circuits affecting lipid mobilization from adipose tissue, such as fasting or postprandial responses. Finally, the selection of amlodipine as a metabolically neutral comparator does not allow distinguishing the contributions of neprilysin inhibition from those of AT_1-receptor blockade to the effects of sacubitril/valsartan observed in this study.

Perspectives

Aberrant renin-angiotensin system activation and NP signaling are not only common in cardiovascular diseases, but are also implicated in metabolic dysfunction. Hence, there is a growing need to recognize the potential metabolic actions of cardiovascular pharmacotherapies, especially those targeting renin-angiotensin system and NP systems. Our study demonstrated that sacubitril/valsartan treatment did not result in clinically relevant changes in exercise-induced abdominal subcutaneous adipose tissue and whole-body lipolysis, energy expenditure and substrate oxidation compared with amlodipine. This finding is relevant because neprilysin substrates, particularly NPs, have been implicated in lipolysis and the pathogenesis of cardiac cachexia. Although the extent to which the present findings can be extrapolated to patients with HF and reduced ejection fraction remains to be elucidated, the lack of changes in exercise-induced lipolysis by sacubitril/valsartan is clinically reassuring. Our findings further support the idea that neprilysin is of lesser importance in regulating NP availability in the vicinity of adipocytes.

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Disclosures

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Novelty and Significance

What Is New?

- Sacubitril/valsartan treatment did not elicit clinically relevant changes in exercise-induced lipolysis or substrate oxidation in obese patients with hypertension.

What Is Relevant?

- An imbalance between fatty acid mobilization and utilization may adversely affect cardiovascular and metabolic health.
- Natriuretic peptides potently augment human adipose tissue lipolysis, postprandial lipid oxidation, and skeletal muscle oxidative capacity, whereas angiotensin II elicits more subtle changes in fatty acid turnover.
- Natriuretic peptides are released during physical exercise and have been suggested to provide lipid fuel to the working skeletal muscle. However, excess natriuretic peptide-mediated lipolysis and its implications in cardiac cachexia have been suggested as potential limitations of neprilysin inhibition. Therefore, the lack of changes in exercise-induced lipolysis by sacubitril/valsartan is clinically reassuring.
- Our study extends previous investigations on the role of neprilysin substrates and angiotensin II type 1 receptors in the regulation of lipid turnover.

Summary

Treatment with sacubitril/valsartan did not elicit clinically relevant changes in exercise-induced lipolysis, energy expenditure, and substrate oxidation in patients with obesity and hypertension compared with amlodipine. These observations further substantiate the hypothesis that neprilysin is of lesser importance in regulating natriuretic peptide availability in the vicinity of adipocytes.