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MINI-REVIEW

Cardiorenal Physiology

Cardiometabolic effects of time-restricted eating

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Abstract

Time-restricted eating (TRE) confines daily caloric intake to 4–10 h, thereby inducing recurrent fasting intervals of 14–20 h. TRE alters meal timing without the need for calorie counting and has been proposed as a simple and sustainable dietary intervention with potential metabolic benefits mediated through circadian alignment and increased amount of time spent in the postabsorptive/fasted state. This mini-review summarizes evidence from randomized controlled trials and meta-analyses on cardiometabolic effects of TRE. Studies indicate a modest weight loss compared with ad libitum eating, but with no consistent benefit when compared with caloric restriction. Effects on glycemic control, insulin sensitivity, and lipid profiles are generally small, variable, and context dependent. The most consistent finding is a lowering of blood pressure by about 4/2 mmHg. The effects of TRE on cardiac function and perfusion are still mostly unexplored, but a 3-wk intervention with alternate-day fasting (∼36 h of fasting) improves myocardial flow reserve and reduces oxygen consumption. In summary, TRE appears to be a feasible dietary intervention, but robust evidence of beneficial effects remains limited. Larger and longer-term studies with clinically relevant cardiometabolic endpoints are needed to determine the clinical efficacy of TRE.

blood pressure; insulin sensitivity; myocardial perfusion; time-restricted eating; weight loss

INTRODUCTION

Definition and Core Principles of Time-Restricted Eating

The global epidemic of obesity, metabolic syndrome, type 2 diabetes (T2D), and chronic kidney disease is driving cardiovascular morbidity and mortality worldwide (1). Conventional lifestyle interventions such as caloric restriction and increased exercise are effective but often difficult to sustain, and pharmacotherapy (such as glucagon-like peptide-1 receptor agonists) can be costly and have side effects—underscoring the need for simple, sustainable long-term strategies (2).

Time-restricted eating (TRE) limits daily caloric intake to between 4 and 10 h, resulting in 14–20 h of daily fasting. Unlike caloric restriction, TRE does not necessarily reduce total energy intake. Instead, it shifts the timing of meals to extend the time spent in the postabsorptive (fasted) state. Other related intermittent fasting regimes are alternate-day fasting (ADF) in which days of ad libitum eating alternate with ∼36 h fasting, and short daily dry fasts (e.g., Ramadan fasting). The terminology used to describe fasting diet interventions has often been inconsistent, and we will adhere to the terminology of fasting proposed by a recent international consensus (3). According to the consensus, TRE is fasting for at least 14 h, and ADF is fasting between 24 and 48 h. A fasting mimicking diet is defined as any diet designed to induce the metabolic effects of fasting while allowing some caloric intake, typically ≤1,000 kcal/day, low in protein and refined carbohydrates, and high in plant-based fats, done for 3–7 days. In contrast, a ketogenic diet is not considered a fasting-mimicking diet, as it is typically not calorie-restricted and has a higher protein and fat content (3, 4). All these diets differ from the eating habits of most adults in the Western world, who spread their food intake over ∼14–15 h/day, leaving only 9–10 h of overnight fast per day (5).

From a clinical perspective, TRE is a feasible and safe intervention that can be applied to almost all individuals regardless of comorbidity (6). The recent RESET trial demonstrated that adherence is generally high (91%) during a 3-mo TRE intervention in individuals with a high risk of T2D, although most participants returned to their baseline eating patterns after the trial ended (6). TRE can be implemented

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without deliberate caloric restriction, although energy intake often decreases spontaneously (7). This raises the question of whether the potential cardiometabolic benefits of TRE primarily reflect caloric restriction, circadian alignment (timing of food intake to circadian rhythms), or repeated induction of a fasted state.

Does Timing Matter? (Early vs. Late TRE)

Beyond the duration of the eating window, the circadian timing of food intake may play a role in the response to TRE. In an early TRE schedule (e.g., 6 h window, 0600–1500), eating takes place in the morning, whereas a late TRE schedule (e.g., 8 h window, 1200–2000) entails eating mostly at dinnertime (Fig. 1). Theoretically, an early eating window may align better with human circadian rhythms, since insulin sensitivity and β-cell secretory capacity peak earlier in the day in healthy individuals (8). Also, splanchnic blood flow redistribution, gastric motility, renal sodium excretion, and natriuresis are increased earlier in the day (9). Late-day food intake is associated with reduced insulin sensitivity, slower postprandial glucose disposal, and blunted natriuretic responses (8, 10–12). However, only a few small randomized controlled trials (RCTs) of short duration have directly compared early versus late TRE (13, 14). These studies suggest that early TRE may improve insulin sensitivity compared with late TRE. Nevertheless, as discussed in *Glucose Levels and Insulin Sensitivity*, whether TRE improves insulin sensitivity at all remains uncertain. Although the proposed effects of circadian timing (early vs. late TRE) are interesting, evidence for these effects is lacking, and direct comparisons between timing of eating windows are limited.

What Happens during Fasting

During fasting, energy metabolism shifts through phases that depend on the duration of food deprivation and the availability of stored substrates. In the early hours of fasting, hepatic glycogenolysis is the predominant source of energy in the form of glucose. Liver glycogen stores are depleted after 12–24 h of fasting (15), after which the preferred substrate for oxidation switches toward fatty acids and ketone bodies. The exact timing of this metabolic switch depends on baseline glycogen stores, physical activity, and individual metabolic phenotype (e.g., T2D and obesity) (16). Ketone bodies provide an alternative source of energy for the heart, brain, and kidneys, and serve as signaling molecules that suppress lipolysis and increase cardiac perfusion (17–19). However, to what extent the potential benefits of ketone bodies influence the response to TRE is uncertain, since the fasting period may not be long enough to induce substantial ketogenesis. Fasting is also associated with natriuresis and alterations in the renin-angiotensin-aldosterone system. The mechanisms underlying these renal and hormonal changes may contribute to the small reductions in blood pressure reported with TRE (20). It should be noted that many of the metabolic and molecular effects of fasting require longer fasting durations. Thus, a recent study demonstrated that approximately 3 days of fasting was necessary to induce a systemic proteomic response (21).

CARDIOMETABOLIC EFFECTS OF TIME-RESTRICTED EATING

We have summarized the main cardiometabolic findings from key randomized controlled trials in Table 1, along with each study's design, duration, population, and comparator.

Body Weight Regulation

A recent meta-analysis of 99 randomized controlled trials (RCTs) including 6,582 adults with a wide range of metabolic phenotypes (healthy, overweight, obesity, T2D, etc.) compared different intermittent fasting strategies with caloric

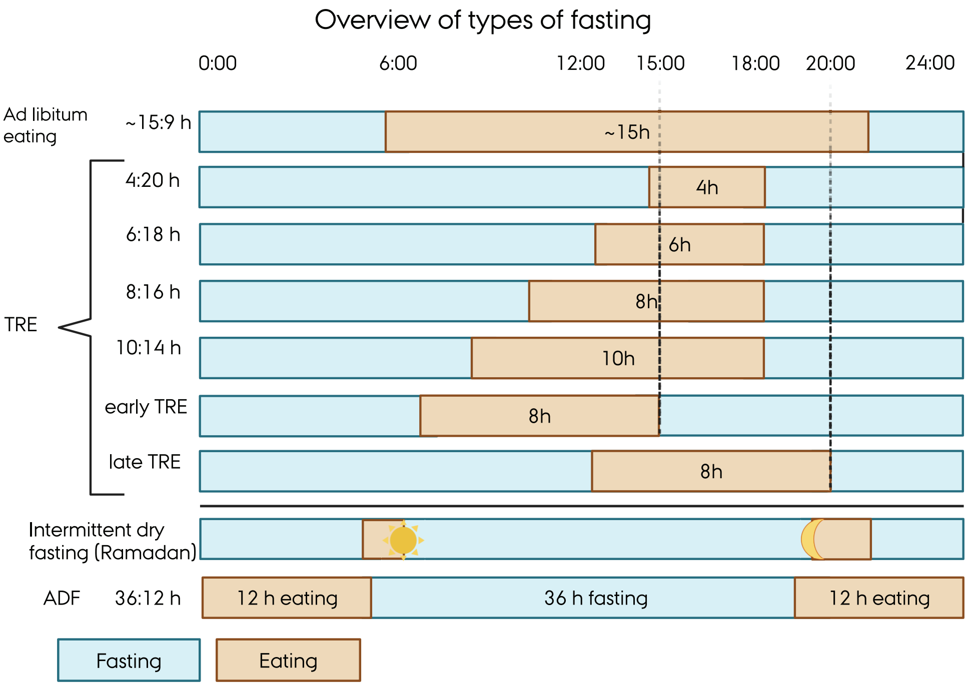

Figure 1. Overview of intermittent fasting patterns. Daily distribution of fasting (blue) and eating (orange) for common regimens including ad libitum eating (~15 h eating/day), time-restricted eating (TRE) with 4–10 h eating windows (examples: 0420, 0618, 0816, and 1014 h) with early- and late-TRE, intermittent dry fasting (Ramadan with sun and moon symbols denoting daylight and night), and alternate-day fasting (ADF with 36 h fasting alternating with 12 h eating). Figure created with a licensed version of BioRender.com.

Table 1. *Overview of the randomized controlled trials discussed in this review*

Study	Population (Condition/ Eligibility), Age, and Baseline BMI	Trial Design	TRE Window	Intervention	Control	Duration	Blood Pressure	Weight	Glycemia/ Insulin Sensitivity	Other Findings
Quist 2024 (6)	High risk of type 2 diabetes (overweight/obesity, prediabetes) 59 (IQR 52–65) years 33.9 ± 5.8 kg/m^2	Parallel-group randomized controlled trial	10 h window (self-selected)	TRE	Control: ad libitum eating	3 mo + 3 months follow-up	ΔTRE-Control: SBP-2 mmHg (95% CI −6 to 2) DBP 0 mmHg (95% CI −3 to 3)	ΔTRE-Control: −0.80 kg (95% CI −1.7 to 0.2)	No improvement in HbA1c or fasting insulin	High adherence during intervention (~91%), but participants tended to return to baseline eating window after the trial.
Pavlou 2023 (7)	Type 2 diabetes 55 ± 12 years 39 ± 7 kg/m^2	Parallel-group randomized controlled trial	8 h window (12–20), fixed eating window	TRE	CR: 25% CR Control: ad libitum eating	6 mo	ΔTRE-Control: SBP −6.0 (95% CI −14 to 1.9) DBP −2.9 (95% CI −8.0 to 2.1) ΔCR-Control: SBP −5.4 (95% CI −13 to 2.4) DBP −1.5 (95% CI −5.5 to 2.4) ΔTRE-CR: SBP −0.6 (95% CI −8.1 to 7.0) DBP −1.4 (95% CI −6.0 to 3.1)	**ΔTRE-Control:** **−3.5 kg (95% CI −6.1 to −0.8)** **−3.6% (95% CI −5.9 to −1.2)** ΔTRE-CR: −1.9 kg (95% CI −4.4 to 0.6) −1.8% (95% CI −4.1 to 0.5)	Change in Hb A1c (%-points): **ΔTRE-control: −0.9%-points (95% CI −1.6 to −0.2)** **ΔCR-control: −0.9%-points (95% CI −1.6 to −0.3)** ΔTRE-CR: 0.04%-points (95% CI −0.6 to +0.7)	TRE led to a spontaneous reduction in energy intake of −**313 (509)** **kcal**/day vs. −**197 (426) kcal/day in CR**. Adherence to TRE: participants kept to their eating window on average 6.1 (0.8) days per week.
Sutton 2018 (10)	Men with prediabetes (overweight/obesity) 56 ± 9 years 32.2 ± 4.4 kg/m^2	Randomized crossover, controlled trial	6 h early window (07–15), fixed eating window	eTRE	Control: 12 h eating window.	5 wk per arm	**ΔTRE-Control:** **SBP −11 ± 4 mmHg** **DBP −10 ± 4 mmHg**	ΔTRE-Control: −0.5 ± 0.3 kg	eTRE decreased insulin resistance **(3-h incremental AUC ratio) by 36 ± 10 U/mg** and increased **insulinogenic index by 14 ± 7 U/mg**	eTRE reduced oxidative stress: **plasma 8-isoprostane decreased by 11 ± 5 pg/mL** (~14% reduction compared to control)
Zhang 2022 (13)	Young adults with overweight/obesity eTRE 23.8 ± 0.6 years lTRE 23.2 ± 0.5 years control 22.1 ± 0.4 years eTRE 27.1 ± 0.7 kg/m^2 lTRE 28.5 ± 0.8 kg/m^2 Control 27.8 ± 0.8 kg/m^2	Parallel-group randomized controlled trial	6 h early (07–13) or late (12–18), fixed eating windows	eTRE and lTRE	Control: Ad libitum eating, >12 h daily eating window	8 wk	**eTRE:** **SBP −5.5 mmHg (95% CI −8.1 to −2.9)** DBP −4.9 mmHg (95% CI −6.8 to −3.1) lTRE:SBP −1.6 mmHg (95% CI −4.3 to 1) DBP −2.0 mmHg (95% CI −3.9 to −0.1) Control: SBP 0.9 mmHg (95% CI −1.8 to 3.7) DBP −4.2 mmHg (95% CI −6.2 to −2.3)	**eTRE:** **−3.5 kg (95% CI −4.2 to −2.9)** **−4.6% (95% CI −5.5 to −3.8)** **lTRE:** **−2.9 kg (95% CI −3.6 to −2.3)** **−3.7% (95% CI −4.6 to −2.9)** Control: −0.2 kg (95% CI −0.9 to 0.5)	eTRE (but not lTRE) reduced mean glucose, fasting insulin, and HOMA-IR at *week 8*.	eTRE increased antioxidant defense: **SOD (an antioxidant enzyme) rose by +3.9 U/mL (95% CI 2.8–4.9)** vs. control +0.8 U/mL (−0.3 to 1.9). No between-group differences in other oxidative stress or inflammation markers (MDA, 8-isoprostane, hs-CRP, TNF-α, IL-6, cortisol).
Xie 2022 (14)	Adults without obesity eTRE 28.7 ± 9.7 years lTRE 31.1 ± 8.4 years control 33.6 ± 11.6 years eTRE 22.7 ± 3.1 kg/m^2 lTRE 21.4 ± 2.2 kg/m^2 Control 21.5 ± 2.9 kg/m^2	Parallel-group randomized controlled trial	≤8 h early window (06–15) ≤8 h late window (11–20), fixed eating window	eTRE and lTRE	Control: ad libitum eating, >8 h daily eating window	5 wk	eTRE: SBP −4.4 ± 9.9 mmHg DBP −3.4 ± 7.2 mmHg lTRE: SBP −5.4 ± 9.6 mmHg DBP −4.7 ± 6.0 mmHg Control: SBP 0.7 ± 7.8 mmHg, DBP 0.0 ± 8.0 mmHg	**eTRE: −1.6 ± 1.4 kg** lTRE: −0.20 ± 2.2 kg Control: 0.30 ± 1.2 kg	eTRE reduced insulin resistance (ΔeTRE-control) **HOMA-IR −1.1 ± 1.6** and **lowered fasting plasma glucose (−0.6 ± 0.8 mmol/L)**.	eTRE reduced inflammatory markers: **TNF-α − 0.81 ± 1.98 pg/mL vs. control 0.39 ± 1.35 and IL-8 − 1.9 ± 4.5 pg/mL vs. + 1.1 ± 2.9**. lTRE did not reduce any of these markers.

Continued

Table 1.— *Continued*

Study	Population (Condition/ Eligibility), Age, and Baseline BMI	Trial Design	TRE Window	Intervention	Control	Duration	Blood Pressure	Weight	Glycemia/ Insulin Sensitivity	Other Findings
Liu 2022 (22)	Adults with obesity TRE 31.6 ± 9.3 years CR 32.2 ± 8.8 years TRE 31.8 ± 2.9 kg/m^2 CR 31.3 ± 2.6 kg/m^2	Parallel-group randomized controlled trial	8 h early window (08–16), fixed eating window	eTRE + 25% CR	Control: 25% CR	12 mo	ΔTRE-CR: SBP −0.3 mmHg (95% CI −3.7 to 3.1) DBP −1.3 mmHg (95% CI −4.1 to 1.6)	ΔTRE-CR: −1.8 kg (95% CI −4 to 0.4)	HOMA-IR: TRE −1.0 (95% CI −1.7 to −0.4), CR −0.5 (−1.1 to 0.1). No additional effect of TRE beyond 25% CR.	No additional effects of TRE beyond 25% CR on body composition, including CT-assessed abdominal visceral fat, subcutaneous fat, and liver fat content.
Jamshed 2022 (23)	Adults with obesity 43 ± 11 years 39.6 ± 6.7 kg/m^2	Parallel-group randomized controlled trial	8 h early window (07–15), fixed eating window	eTRE and CR (−500 kcal/-day below resting energy expenditure)	Control: eating window ≥12 h + CR (−500 kcal/day below resting energy expenditure)	14 wk	ΔeTRE-CR: SBP −4.0 mmHg (95% CI −9.0 to 1.0) **DBP −4.0 mmHg (95% CI −8.0 to 0.0)**	**ΔTRE-CR:−2.3 kg (95% CI −3.7 to −0.9)−1.5% (95% CI −2.7 to −0.2)**	HOMA-IR change: **eTRE -2.00 (95% CI −3.24 to −0.76)** vs. control −0.74 (−2.02 to 0.54, Δ (eTRE - control) −1.10 (−2.90 to 0.70). No additional effect on fasting glucose ΔeTRE-control (−2 mg/dL (95% CI −9 to 5)	eTRE **improved mood (lower total mood disturbance, higher vigor-activity, lower fatigue-inertia, and lower depression-dejection)**. Other mood domains and sleep outcomes were similar between groups.
Oldenburg 2025 (24)	Adults with obesity TRE 44.0 ± 11.5 years CR 42.2 ± 9.6 years Control 43.4 ± 10.7 TRE 35.8 ± 5.7 kg/m^2 CR 36.5 ± 5.5 kg/m^2 Control 36.4 ± 4.1 kg/m^2	Parallel-group randomized controlled trial	8 h self-selected window	TRE	CR: 15% CR Controls: ad libitum eating	12 wk	ΔTRE-CR: SBP 0.80 mmHg (95% CI −21 to 22) DBP −3.6 mmHg (95% CI −17 to 9.7) ΔTRE-Control:SBP −5.0 mmHg (95% CI −26 to 16) DBP −2.2 mmHg (95% CI −15 to 11) ΔCR-Control:SBP −5.8 mmHg (95% CI −29 to 17) DBP 1.4 mmHg (95% CI −13 to 15)	TRE: −3.0 kg (95% CI −4.8 to −1.3) CR: −4.1 kg (95% CI −6.0 to −2.2) Control: −1.6 kg (95% CI −3.6 to 0.3) ΔTRE-Control: −1.4 kg (95% CI −4.5 to 1.7)	No between-group differences in glycemic measures, including HbA1c, HOMA-IR, clamp-derived insulin sensitivity, and CGM time-in-range.	High-dose clamp metabolic flexibility (insulin-induced shift in substrate oxidation): **Δ(TRE-CR) −0.04 (95% CI −0.08 to −0.002).**
Jamshed 2019 (25)	Adults with overweight/ obesity 32 ± 7 years 30.1 ± 2.7 kg/m^2	Randomized crossover-controlled trial	6 h early window (08–14), fixed eating window	eTRE	Control: 12 h eating schedule (08–20)	4 days per arm	Not reported	Weight maintained	CGM: **24-h mean glucose −4 ± 1 mg/dL** vs. control and **MAGE −12 ± 3 mg/dL. Fasting glucose −2 ± 1 mg/dL, insulin −2.9 ± 0.4 mU/L, HOMA-IR −0.7 ± 0.1 vs. control.**	eTRE **increased SIRT1 (10 ± 3%, *P* = 0.004) and LC3A (22 ± 5%, in the morning and increased MTOR 9 ± 3%, in the evening.** ATG12 was elevated 5 ± 2% but not significantly after multiple-comparison correction.

For Zhang et al. (13) and Xie et al. (14), blood pressure data are reported as within-group changes from baseline, as between-group differences were not reported in the original publications. Values in bold indicate outcomes reported by the original authors as statistically significant between groups. Unless otherwise stated, data are presented as means ± SD Median (IQR) is reported where indicated. Δ denotes a between-group difference in change from baseline. ATG12, autophagy related 12; AUC, area under the curve; BMI, body mass index; CGM, continuous glucose monitoring; CI, confidence interval; CR, calorie restriction; DBP, diastolic blood pressure; eTRE, early time-restricted eating; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LC3A, microtubule-associated proteins 1 A/1B light chain 3 A; IL-6, interleukin 6; IL-8, interleukin 8; lTRE, late time-restricted eating; MAGE, mean amplitude of glycaemic excursions; MDA, malondialdehyde; MTOR, mechanistic target of rapamycin; SBP, systolic blood pressure; SIRT1, sirtuin 1; SOD, superoxide dismutase; TNF-α, tumor necrosis factor alpha; TRE, time-restricted eating.

restriction or ad libitum eating (26). ADF was the only strategy that produced additional weight loss compared with caloric restriction (~1.3 kg), whereas TRE led to a modest reduction (~1.7 kg) versus ad libitum intake (26). Weight loss across studies appears largely explained by reductions in energy intake, with no substantial changes in body composition (27).

The meta-analysis did not explore whether TRE is associated with weight loss independently of concurrent caloric restriction, and results from individual RCTs are mixed. In a 12-mo RCT of 139 adults with obesity, TRE (8 h) combined with caloric restriction did not result in a greater weight loss than caloric restriction alone (22). In contrast, a 14-wk trial in 90 adults with obesity showed an additional 2.3-kg weight loss with TRE (≤8 h) plus caloric restriction and exercise versus ≥12 h eating plus caloric restriction and exercise (23). Similarly, in adults with T2D, a 6-mo RCT found a greater weight loss with TRE (8 h) compared with 25% caloric restriction (−3.6% vs. −1.8% of body weight) (7). By contrast, a 12-wk trial in 88 adults with obesity reported no significant effect of TRE (8 h) without caloric restriction on weight or body composition (24). Also, a 3-mo intervention with TRE (10 h) did not cause individuals at high risk of T2D to lose weight (6).

In summary, TRE may induce modest weight loss, but it is unclear to what extent this is caused by concomitant caloric restriction.

Glucose Levels and Insulin Sensitivity

It has been proposed that TRE may improve glycemic control independent of weight loss, but the overall evidence is mixed, and any effects appear to be modest, variable, and context-dependent. In a 5-wk crossover study in men with prediabetes, early TRE (6 h) improved oral glucose tolerance test-derived indices of β-cell function and insulin sensitivity (10). Similarly, early TRE (6 h) lowered 24-h glucose levels and excursions in a 4-day crossover trial (25). These positive findings come from short-term studies in specific populations, and longer studies have produced more mixed results. Thus, a 3-mo TRE (8–10 h) study did not result in decreased glycated hemoglobin (HbA1c) in individuals at high risk of T2D (6), whereas a 6-mo TRE (8 h) study in adults with T2D resulted in comparable reductions of HbA1c between outright caloric restriction and TRE without caloric restriction (7). In adults with obesity but without diabetes, a 12-wk RCT comparing TRE (8 h) with 15% caloric restriction and unrestricted eating found no between-group differences in HbA1c, homeostasis model assessment of insulin resistance (HOMA-IR), continuous glucose monitoring, or insulin sensitivity estimated by a hyperinsulinemic-euglycemic clamp (24). This is also supported by a recent meta-analysis, investigating a wide range of metabolic phenotypes, which showed no effect of TRE on HbA1c or HOMA-IR when compared with caloric restriction, but a minor decrease in HOMA-IR when compared with ad libitum eating (26).

The improvements in fasting insulin and HbA1c described in some studies (7, 22) may well be secondary to weight loss, since effects on glucose levels are smaller or absent in studies without weight loss (10, 25, 28). In another recent meta-analysis of 18 studies ($n = 1{,}169$, 16 RCTs, including 2 crossovers, and 2 non-RCTs) with a duration of 4–14 wk, TRE did not lower fasting glucose, but was associated with discrete reductions in HbA1c and fasting insulin, particularly when the eating window was early in the day (28). In summary, any weight-independent effects of TRE on glycemic control and insulin sensitivity appear small, variable, and context dependent.

Lipid Profiles

The impact of TRE on circulating lipids is also inconsistent. A 5-wk study of early TRE (~6 h) found no difference in a standard lipid panel compared with a standard diet (10). In addition, TRE (8–10 h) did not change fasting lipids in individuals with high risk of T2D (6).

A meta-analysis stratified by eating window length found contrasting results with an increase in total cholesterol after a shorter eating window (7–9 h) and a decrease with a longer eating window (10–12 h). Triglyceride levels were only reduced with longer eating windows, and no effects on low-density and high-density lipoprotein cholesterol levels were observed (29). Overall, current evidence does not support any clinically relevant effect of TRE on circulating lipids.

Blood Pressure and Renal Effects

Although the effects on weight, glycemic control, and lipid profiles are very small or even absent, the cardiovascular effects of TRE appear to be more promising. Across trials, TRE produces small to moderate reductions in blood pressure, with the magnitude of the effect depending on the timing of the eating window and study design. In an early TRE crossover trial (6 h, 5 wk), morning systolic blood pressure fell by ~11 mmHg and diastolic blood pressure ~10 mmHg, despite no weight loss (10). In a 14-wk RCT, early TRE (8 h) in combination with caloric restriction lowered diastolic blood pressure by −4 mmHg (23). A meta-analysis of ~12-wk TRE interventions showed a pooled reduction in systolic blood pressure of −4.15 mmHg (95% CI −6.7 to −2.3) and diastolic blood pressure −2.06 mmHg (95% CI −4.16 to 0.02) (30). However, blood pressure after discontinuation of TRE has not been systematically assessed in randomized trials, and therefore, the durability of the blood pressure effects remains uncertain. Below, potential renal and circadian mechanisms that may contribute to these blood pressure effects are outlined.

At the renal level, any hemodynamic effects of TRE are likely small and may relate to circadian variation in filtration and sodium handling. Together, this may contribute to the modest blood pressure reductions observed with TRE, while effects on glycemic control remain small (20, 31–33).

Glomerular filtration rate, tubular sodium handling, and renin-angiotensin-aldosterone system activity all have diurnal variation, with higher daytime filtration and natriuresis and a nocturnal decline (31). Circadian misalignment (late eating, shift work schedule) may affect these rhythms and are associated with hypertension and progression of chronic kidney disease (34). Experimental evidence from a rodent model also shows that knockout of a circadian clock transcription factor (period circadian regulator 1) in the kidney increases sodium retention in response to a high-salt diet (35, 36). Therefore, it can be speculated that food intake earlier in the day, where natriuresis is higher, may synchronize feeding-fasting cycles with the kidney's intrinsic clock, with an increased daytime natriuresis (37).

In addition, concentrating meals (and insulin peaks) within the daytime window increases insulin-mediated tubular sodium reabsorption during a shorter window of feeding, whereas the prolonged overnight fast lowers insulin levels, which reduces tubular sodium reabsorption, for example via sodium-hydrogen exchanger 3 and epithelial sodium channel, and increases sodium delivery to the macula densa, which may transiently suppress renin release and thereby increases natriuresis. This shift in sodium handling may result in a net diuretic effect, potentially contributing to the modest blood pressure reductions observed with TRE (20, 31–33).

In summary, the evidence supports that TRE reduces blood pressure to an extent that may be clinically significant, and that the effects appear to be more pronounced with earlier and shorter eating windows (29, 38, 39).

Cardiac Perfusion and Substrate Metabolism

During recent years, there has been an interest in the cardiac effects of ketone bodies, including interventions that increase ketone levels, such as fasting diets. Most TRE trials do not report circulating ketone concentrations, but in the few that do, reported fasting-morning ketone level increases are small (0.03 mmol/L larger than controls, to a concentration of 0.15 mmol/L) and remain well below the levels observed with alternate-day fasting (0.69 ± 0.09 mmol/L on fasting days and 0.2 ± 0.03 mmol/L in the 12 h eating window) or with a ketogenic diet (1.12 ± 0.91 mmol/L after an overnight fast) (25, 40, 41).

We have previously found that a ketone body infusion raising blood concentrations to 3.88 ± 0.5 mmol/L can halve myocardial glucose uptake and increase resting myocardial blood flow by ∼75% (17). Subsequent studies have confirmed that ketone body supplementation can improve cardiac output in heart failure (42–44).

The important question is whether some of these potentially beneficial cardiovascular effects can be achieved with TRE or other fasting diets such as ADF or a fasting-mimicking diet.

We have recently published a paper investigating the effect of ADF on myocardial perfusion, oxygen consumption, and substrate metabolism (40). ADF (36-h fasting) represents a substantially more prolonged fasting exposure than TRE, and

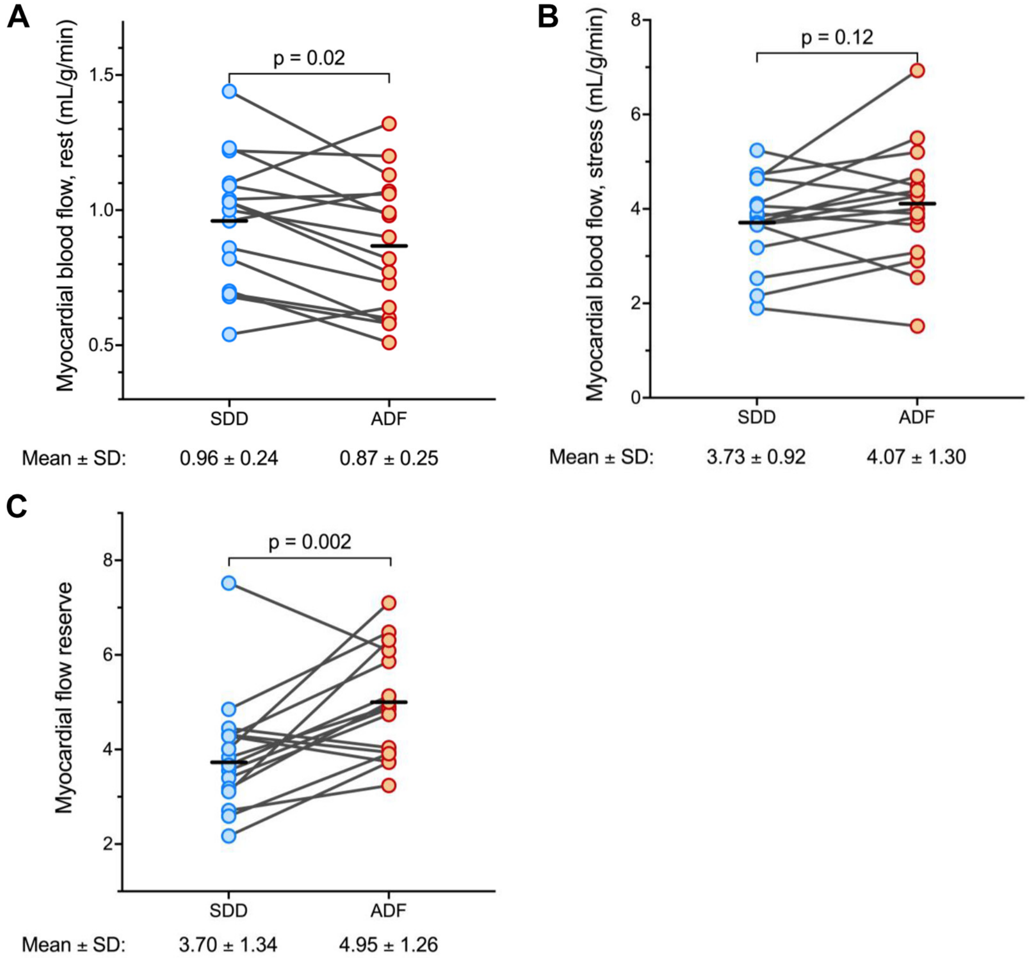

Figure 2. Effects of alternate-day fasting on myocardial perfusion and flow reserve. After 3 wk of ADF in $n = 16$ adults with overweight, resting myocardial blood flow (MBF) decreased by 9 ± 3% (*A*) and adenosine stress MBF tended to increase by 9 ± 5% (NS) (*B*), yielding a 34 ± 8% increase in myocardial flow reserve (*C*) measured by $[^{15}O]H_2O$ positron emission tomography/computed tomography (PET/CT) ($P < 0.01$). Data are shown as means ± standard error of the mean (SEM) for paired comparisons. Panels *A*–*C* are reproduced from Ref. (40) [Kjærulff et al. Used with permission of Oxford University Press on behalf of the Endocrine Society (via RightsLink)]. ADF, alternate-day fasting.

these findings should therefore be regarded strictly as hypothesis-generating observations from an extended fasting paradigm, not as direct evidence for TRE effects. Importantly, the physiological and metabolic responses to ADF cannot be extrapolated to TRE, and whether shorter daily fasting windows confer similar cardiovascular effects remains unknown. In our study, we studied 16 individuals with overweight in a 3-wk RCT. Here, we observed a 10% reduction in myocardial oxygen consumption and a lowering of blood pressure by 13/9 mmHg. This was accompanied by a remarkable 34% increase in myocardial flow reserve (MFR), which is a measure of the capacity to increase coronary circulation during maximal vasodilation (Fig. 2). The increase in MFR was driven by a ∼9% decrease in resting myocardial blood flow and a stress myocardial blood flow that tended to be higher, consistent with hemodynamic unloading and increased vasodilatory capacity (40). However, no difference was observed in ketone, free fatty acid or glucose uptake in the heart.

MFR is an established independent prognostic marker of cardiovascular mortality, in a cohort of 12,594 individuals, each 0.1-unit decrease in MFR was associated with ∼9% higher hazard of death (45). The magnitude of the MFR increase observed with ADF (∼34%) is comparable to that reported with statin therapy (∼18%) and β-blockade (∼46%) (46–48). However, whether such improvements are sustained over time or achievable with shorter fasting durations typical of TRE remains to be determined.

Our findings with ADF (40), contrast with our recent study of the cardiovascular effects of a ketogenic diet (41). Here, we did not observe any change in myocardial perfusion, oxygen consumption, or MFR, but instead observed a substrate shift with a 26% reduction in free fatty acid oxidation, presumably due to a shift toward ketone body oxidation (41). Taken together, these studies provide limited clinical evidence on myocardial perfusion and energetics across distinct dietary interventions. Mechanistic interpretation should therefore be cautious.

Collectively, these findings suggest that a prolonged fasting regimen such as ADF can reduce cardiac oxygen demand and improve vasodilatory reserve, whereas a ketogenic diet does not produce the same cardiac effects, suggesting that cardiovascular effects of prolonged fasting may not be solely contingent on ketone concentrations. However, whether shorter daily fasting durations typical of TRE, where ketone concentrations increase only modestly and transiently, can induce comparable cardiovascular adaptations remains unknown.

This represents an important knowledge gap, and a planned trial is aiming to address this question in part, by investigating the effect of TRE on vascular and endothelial function using flow-mediated vasodilation as an exploratory outcome (49). To our knowledge, no TRE trials have explored the effects of TRE on myocardial perfusion or oxygen consumption.

CONCLUSIONS AND FUTURE DIRECTIONS

The current evidence supporting the cardiometabolic benefits of TRE is limited, and it is possible that clinically meaningful effects may be modest when the fasting period is less than 24 h. The most consistent finding from short-duration RCTs and meta-analyses is modest reductions in blood pressure, whereas effects on weight, glucose, lipid profiles, and insulin sensitivity are generally small and inconsistent (10, 28, 30). Importantly, longer-term data are scarce, and key mechanistic and vascular endpoints remain insufficiently studied, including endothelial function, oxidative stress, and inflammatory biomarkers. In addition, evidence for potential effect modification by sex, age, or circadian timing of the eating window is lacking, and potential differences remain uncertain. Future trials should prioritize patient populations at elevated cardiometabolic risk (e.g., hypertension or type 2 diabetes) and examine dose-response effects of fasting duration and timing (early vs. late TRE). Further studies with extended follow-up are needed to determine whether any observed blood pressure lowering is sustained during continued TRE and after the intervention ends. Adequately powered trials with blood pressure outcomes, ideally assessed by ambulatory blood pressure monitoring, are needed to clarify the magnitude and durability of any effect. Nevertheless, even modest reductions in blood pressure may be clinically significant: a ∼5 mmHg decrease in systolic blood pressure is associated with 10% lower risk of major cardiovascular events, including 13% lower stroke incidence, 8% lower ischemic heart disease risk, and 5% lower cardiovascular mortality (50).

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.M.S., M.L.G.K., L.C.G., and E.S. prepared figures; A.M.S. and E.S. drafted manuscript; A.M.S., M.L.G.K., L.C.G., and E.S. edited and revised manuscript; A.M.S., M.L.G.K., L.C.G., and E.S. approved final version of manuscript.

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