Oral Consumption of Vitamin K_2 for 8 Weeks Associated With Increased Maximal Cardiac Output During Exercise

Brian K. McFarlin, PhD, FACSM, FTOS; Andrea L. Henning, MS; Adam S. Venable, PhD

ABSTRACT

Background • Vitamin K_1 and K_2 are not typically common in a Western diet because they are found in a variety of fermented foods. Vitamin K_2 in particular has been demonstrated to restore mitochondrial function and has a key role in production of mitochondrial adenosine triphosphate. Thus, it is reasonable to speculate that dietary supplementation with vitamin K_2 could increase the function of muscle with high mitochondrial content (ie, skeletal and cardiac muscle).

Objective • The purpose of this study was to determine if 8 wk of dietary supplementation with Vitamin K_2 could alter cardiovascular responses to a graded cycle ergometer test.

Design • The study was a randomized controlled trial.

Setting • The study took place in the Applied Physiology Laboratory of the Department of Biological Sciences at the University of North Texas (Denton, TX, USA).

Participants • Participants were aerobically trained males and female athletes (N = 26).

Intervention • Participants were randomly assigned either to a control group that received a rice flour placebo or to an intervention group that received vitamin K_2. For weeks 1 to 4, participants received 300 mg/d; for weeks 5 to 8, they received 150 mg/d. Subjects assigned to the control group received similar doses to mirror the intervention group. Subjects consumed the supplements during an 8-wk period while they maintained their typical exercise habits.

Outcome Measures • At baseline and postintervention, participants completed a standard, graded exercise test on an electronically braked cycle ergometer. Before the test, participants were fitted with a mouth piece, and their oxygen consumption, carbon dioxide production, respiratory rate, and respiratory exchange ratio were measured. In addition, participants were fitted with skin-mounted electrodes that measured noninvasive cardiac output, stroke volume, and heart rate. To assess the cumulative exercise change, an area-under-the-curve (AUC) value was calculated separately for each outcome variable at each treatment time point.

Results • Vitamin K_2 supplementation was associated with a 12% increase in maximal cardiac output, with $P = .031$, with a trend toward an increase in heart-rate AUC, with $P = .070$. No significant changes occurred in stroke volume.

Conclusions • Although vitamin K_2 supplementation has previously been reported to improve cardiovascular function in diseased patients, to the research team's knowledge, the current study is the first to report its potential in active individuals. More research is needed to fully evaluate the potential effects of the observed effects. (*Altern Ther Health Med.* 2017;23(4):26-32)

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Vitamin K exists in 2 primary forms, which differ in their bioactivity and dietary abundance.[1] Vitamin K_1, also known as phylloquinone, is found in a variety of plant-based foods but is much less bioactive than vitamin K_2. Vitamin K_2 is a family of related compounds, also

known as menaquinones, that are produced by bacteria during the process of fermentation.[2]

Menaquinones have been reported to reduce calcium accumulation in vascular walls,[3-7] induce tumor cell apoptosis,[8,9] and restore the production of mitochondrial adenosine triphosphate (ATP).[10,11] The later effect has direct implications for the contractile muscles that have high levels of mitochondria (ie, cardiac muscles). In humans, menaquinone-7 is in relatively low abundance in Western diets because it is primarily found in fermented foods and, to a much lesser extent, in meat and dairy products.[2,3] Despite the fact that the US Department of Agriculture recognizes menaquinones from bacterial fermentation as a Generally Recognized as Safe ingredient, they are not commonly found in Western diets.[2]

With respect to heart disease, increased dietary vitamin K_2 results in the carboxylation of osteocalcin and matrix gamma-carboxyglutamic protein, which increases bone calcium storage, while it prevents the accumulation of excess calcium in vascular soft tissue.[4-7] The latter is a common side effect associated with increased dietary calcium supplementation and increases the risk of heart disease.

Schurgers et al is considered one of the foremost researchers in the area of K_2 supplementation and vascular health and has demonstrated consistently the ability of K_2 supplementation to alter plaque stabilization and reversal.[5,6,12] In bacteria, vitamin K_2 mediates electron transfer; however, it is unknown if that effect is maintained upon uptake of vitamin K_2 by eukaryotic cells. Some studies have shown that vitamin K_2 in *Drosophila* has the capacity to exert the same electron transfer actions as ubiquinone in the mitochondria.[10,11] Thus, vitamin K_2 may have the ability to restore mitochondrial function when ubiquinone is limited or disrupted.

Given the role of vitamin K_2 in mitochondrial function, it is plausible to speculate that it may also be effective in other physiological conditions that limit mitochondrial function. Maximal aerobic exercise represents a physiological stimulus that is often limited by the ability of the heart to continue pumping blood at a high rate. In highly trained individuals, it is actually common for maximal heart rate to decline with increased training, mostly as a function of increased blood volume and the associated increase in stroke volume. Decreased maximal heart rate is a side effect of training that may reduce the ability of an individual to maximize cardiac output to his or her physiological limit.[13,14]

It is reasonable to speculate that dietary treatment with vitamin K_2 can improve cardiac mitochondrial function, which may reverse training-induced reductions in maximal heart rate and/or improve stroke volume. The combination of these effects may result in an improved cardiac output during graded exercise.

To current research team's knowledge, no published reports have examined the ability of vitamin K_2 supplementation to improve cardiovascular function during maximal aerobic exercise in active individuals. The purpose of the current study was to determine the effects of 8 weeks of oral supplementation with vitamin K_2 on heart rate, stroke volume, cardiac output, oxygen consumption, blood lactate, and ventilation.

METHODS

Participants

The study took place at the Applied Physiology Laboratory of the Department of Biological Sciences at the University of North Texas (UNT; Denton, TX, USA). Participants were aerobically trained males and female athletes, who were selected from a larger pool of 70 individuals who had expressed interest in the study after seeing posted flyers or hearing an announcement. From that larger pool, 26 participants met all inclusion and exclusion criteria.

To participate, potential participants were required (1) to be free of metabolic and inflammatory disease; (2) to not be regular consumers of fermented foods, such as cheese and soybeans; (3) to be of normal body composition as shown on both a body mass index (BMI) and a dual-energy X-ray absorptiometry (DXA) scan; and (4) to be recreationally active as defined by exercise logs and an above-average VO_2 peak for their age and gender groups.

Potential participants were scheduled for a time to report to the laboratory to be screened. Screening consisted of the completion of a standard medical history form, a log of exercise habits, BMI and DXA scans to determine body composition, and a graded maximal exercise test on a cycle ergometer.

The screening procedures used in this study were consistent with procedures that the current research team has used and have been described in detail in other studies.[15-18] Potential participants who met the criteria were scheduled for additional testing. Participants' characteristics are provided in Table 1.

Table 1. Participant Characteristics at Baseline

Variable	Control Group (n = 13) Mean ± SE	Intervention Group (n = 13) Mean ± SE
Gender, No. of men	3	5
Age, y	20 ± 1	21 ± 1
Height, m	1.66 ± 0.09	1.72 ± 0.08
Weight, kg	62.4 ± 11.4	66.6 ± 11.0
BMI	22.7 ± 9.7	22.4 ± 2.1
Body fat %	26.4 ± 9.7	20.6 ± 9.4
VO_{2max}, mL/kg/min	43.88 ± 2.87	46.36 ± 3.13

Abbreviations: SE, standard error of the mean; BMI, body mass index.

All procedures described in this article were reviewed and approved by the UNTs institutional review board for human subjects research. All testing was conducted in accordance with the latest edition of the Declaration of Helsinki. After expressing interest in participating, subjects gave verbal and written consent to participate.

Procedures

Pilot Study. Oral vitamin K_2 supplementation has been previously studied for its ability to counter cardiovascular disease (CVD) during increased calcium intake and to restore mitochondrial function. Those 2 effects led the current research team to speculate that vitamin K_2 supplementation might have the potential to further augment changes in cardiovascular function induced by exercise training.

To test that hypothesis initially, the research team completed a pilot study (N = 15) using a commercially available form of vitamin K_2 derived from menaquinone-7 (MyoMax, Nu Science Trading, Phoenix, AZ, USA). As described in the introduction, menaquinone-7 has been speculated to be the most bioactive form of vitamin K_2 in humans.[1,2]

For the pilot study, participants were randomly assigned either to a control (placebo) or intervention (vitamin K_2) group for 8 weeks. The effectiveness of the dosing was confirmed via the measurement of participants' ratio of undercarboxylated to overcarboxylated osteocalcin (data not shown). A graded maximal exercise test was completed on a cycle ergometer at baseline and postintervention to assess the changes in the cardiovascular variables.

From the pilot study, the research team found trends toward an increased area-under-the-curve (AUC) for heart rate during a graded exercise test (effect size = 0.30) and increased maximal cardiac output (effect size = 0.32) for vitamin K_2 compared to placebo. The team did not observe any trends toward an alteration in stroke volume as a result of regular training, which was the placebo condition, or supplementation. Based on the responses observed in the pilot study, the team determined that the study needed a minimum of 26 participants to achieve a minimum of 80% statistical power for detection of AUC for heart rate and maximal cardiac output for vitamin K_2 treatment compared to placebo.

Current Study. Participants were randomly assigned either to the control (rice flour placebo) or intervention (vitamin K_2) group using double-blind procedures. The group assignments were coded (ie, random number assigned to treatment vs control by the manufacturer), and members of the UNTs staff were not unblinded until all testing procedures were completed and a final raw data set had been generated. Subjects consumed either the intervention or control supplement while maintaining their regular exercise/physical activity habits. Subjects were not prescribed a specific training intervention that they were required to adhere to.

Intervention

For the intervention group, dosing was accomplished in 2 phases during an 8-week period. The loading phase was completed in weeks 1 to 4, during which participants received 300 mg/d of vitamin K_2, and the maintenance phase was completed in weeks 5 to 8, during which participants received 150 mg/d of the supplement. The loading and maintenance doses supplied 320 mcg/d and 160 mcg/d of vitamin K_2, respectively. Supplements were consumed with food at generally the same time each day. For the control group, subjects received rice flour in place of the vitamin K_2 supplement using the exact same number of capsules and supplementation schedule as the intervention group. At no time during the study did any participant report an adverse effect to taking the supplement or the placebo.

Outcome Measures

Measurements occurred at baseline and postintervention after the 8 weeks of supplementation for all tests.

Experimental Exercise Test. Participants completed an experimental exercise test that consisted of 24 minutes of discontinuous, incremental exercise test on a cycle ergometer (Lode Excalibur Sport, Groningen, Netherlands). The test included six 4-minute exercise stages, each with 3 minutes of exercise and 1 minute of passive recovery. Exercise resistance (ie, the wattage on the cycle ergometer) was increased gradually in a manner designed to achieve a VO_2 peak by the conclusion of the sixth exercise stage. Cardiovascular measurements were made continuously and finger-stick blood samples were collected at the completion of each exercise interval for the measurement of blood lactate (Lactate Plus, Nova Biomedical, Waltham, MA, USA).

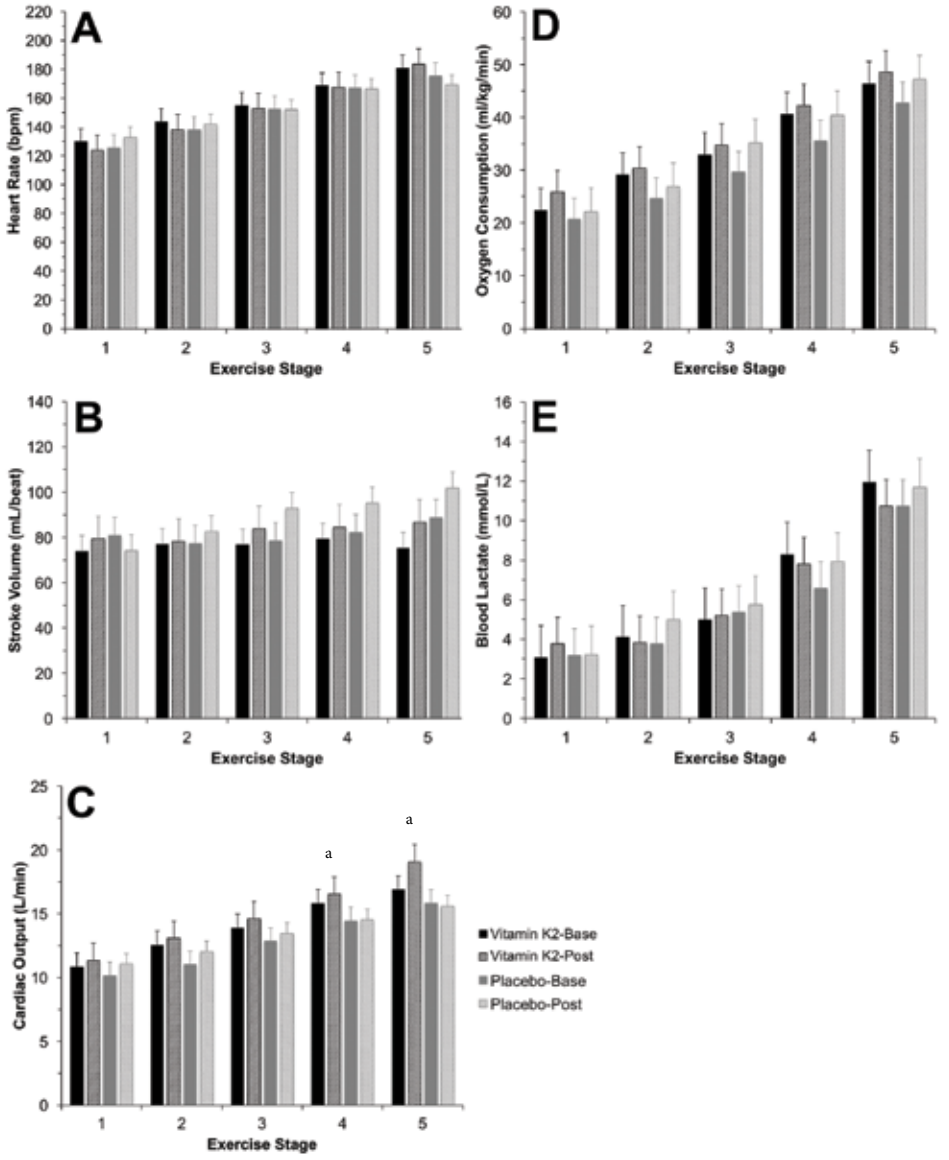
Cardiovascular Measurement. Prior to testing, participants were fitted with skin-mounted electrodes for the noninvasive measurement of heart rate, stroke volume, and cardiac output (Physioflow Enduro, Poissy, France). In addition, they were fitted with a neoprene mask and connected to a metabolic cart for the measurement of oxygen consumption, ventilation, and the respiratory exchange ratio during exercise (MGC Diagnostics, Saint Paul, MN, USA). Data were collected and analyzed using the software provided by the manufacturers.

Calculation of AUC. To assess the cumulative exercise change, an AUC value was calculated separately for each outcome variable at each treatment time point, using a previously described method by the current research team.[19] These calculations resulted in the consolidation of 14 time-point measurements down to 2. To standardize the response to the same scale for visualization, AUC values were log transformed. The baseline AUC of the control and intervention groups was similar; therefore, the research team graphed only the response following 8 weeks of supplementation.

Statistical Analysis

Prior to formal statistical analysis, the data were analyzed for normality and constant error variance using the explore

Figure 1. Comparison among absolute change in heart rate (A), stroke volume (B), cardiac output (C), oxygen consumption (D), and blood lactate (E). Subjects were randomized to either a vitamin K_2 or control (rice flour) condition. They completed a discontinuous, graded exercise test on cycle ergometer prior to and after 8 wk of exercise training consuming either a specific supplement.



[a]Indicates a significant ($P < .05$) increase in cardiac output with vitamin K_2 supplement following 8 wk. Small, nonsignificant were present for stroke volume, particularly at stages 4 and 5.

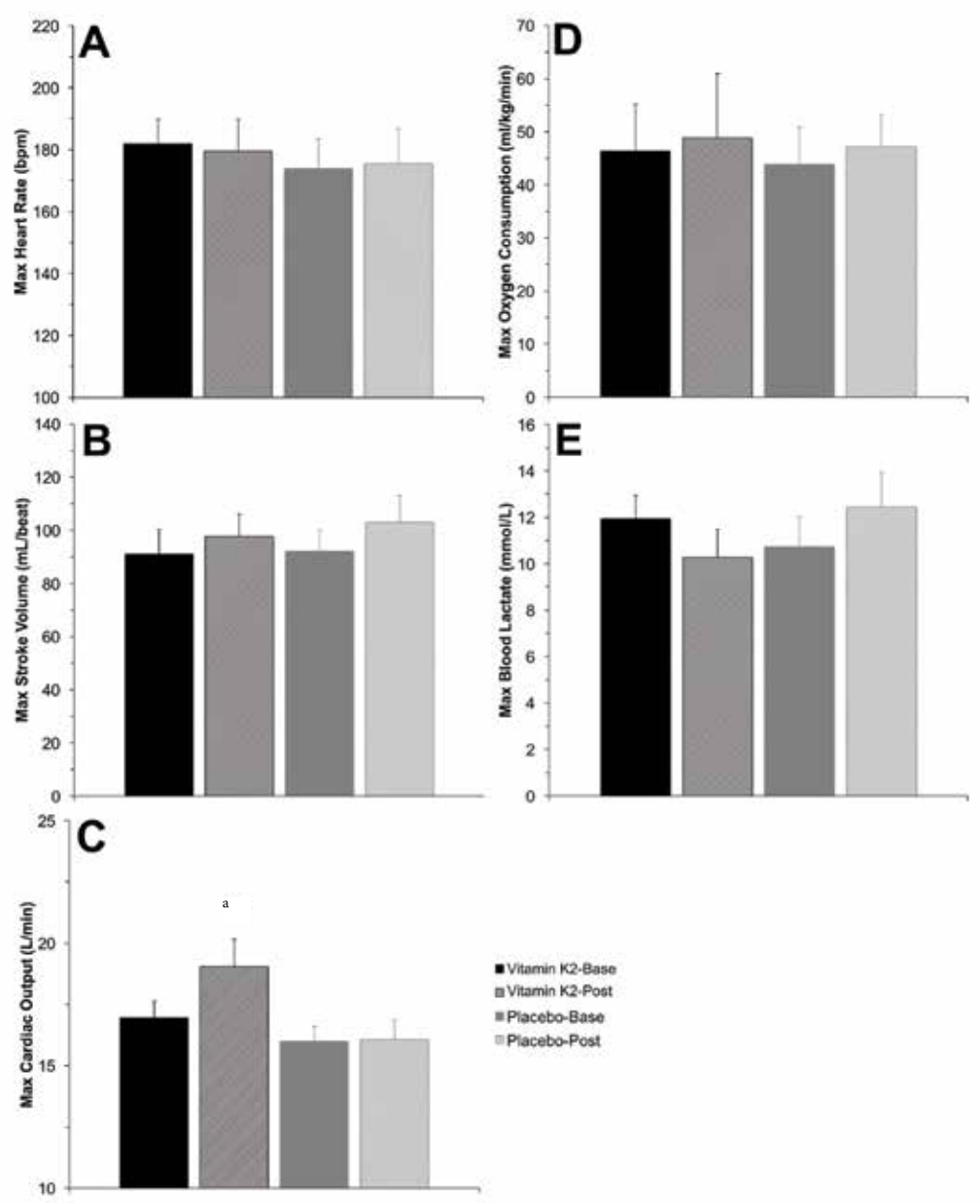
function in SPSS, version 22 (IBM, Armonk, NY, USA). Outcome variables were analyzed separately for significance using an analysis of variance (ANOVA) with repeated measures on the second and third factors—group by treatment time by exercise time—pre, stage 1, stage 2, stage 3, stage 4, stage 5, and stage 6. Calculated AUC values were compared using a group by treatment time ANOVA with repeated measures on the second factor. Significance was set at $P < .05$. A Tukey post hoc test was used where needed to identify the comparison responsible for significant main or interaction effects.

RESULTS

Absolute Changes

On an absolute basis, the study found a significant, 12% increase in maximal cardiac output with vitamin K_2 compared to the placebo ($P = .031$). The maximal cardiac outputs were achieved at either stage 5 or 6 of exercise (ie, near the maximal stages). See Figure 1 and Figure 2. The research team also observed small, but ultimately nonsignificant, changes in heart rate (Figure 1A and Figure 2A) and stroke volume (Figure 1B and Figure 2B) for the intervention compared to the control group.

Figure 2. Compares the maximal response for heart rate (A), stroke volume (B), cardiac output (C), oxygen consumption (D), and blood lactate (E). Subjects were randomized to either a vitamin K_2 or control (rice flour) condition. They completed a discontinuous, graded exercise test on cycle ergometer prior to and after 8 wk of exercise training consuming either a specific supplement.



[a]Indicates a significant ($P < .05$) increase in maximal cardiac output with vitamin K_2 supplement following 8 wk. Small, nonsignificant increases in maximal stroke volume and decreases in blood lactate were observed.

Although not significant, the observed changes in heart rate and stroke volume may explain the observed significant changes in maximal cardiac output with vitamin K_2 treatment. The research team did not observe any significant group or exercise response differences for oxygen consumption (Figure 1D and Figure 2D). That response was not unexpected because the participants in the study were fairly well trained, and as such, their tests typically would not show increased oxygen consumption. The research team observed a potentially interesting trend where maximal blood lactate was lower from supplementation with vitamin K_2 compared to the placebo (Figure 1E and Figure 2E). A full list of means and standard errors for key outcome variables is presented in Table 2.

AUC Response

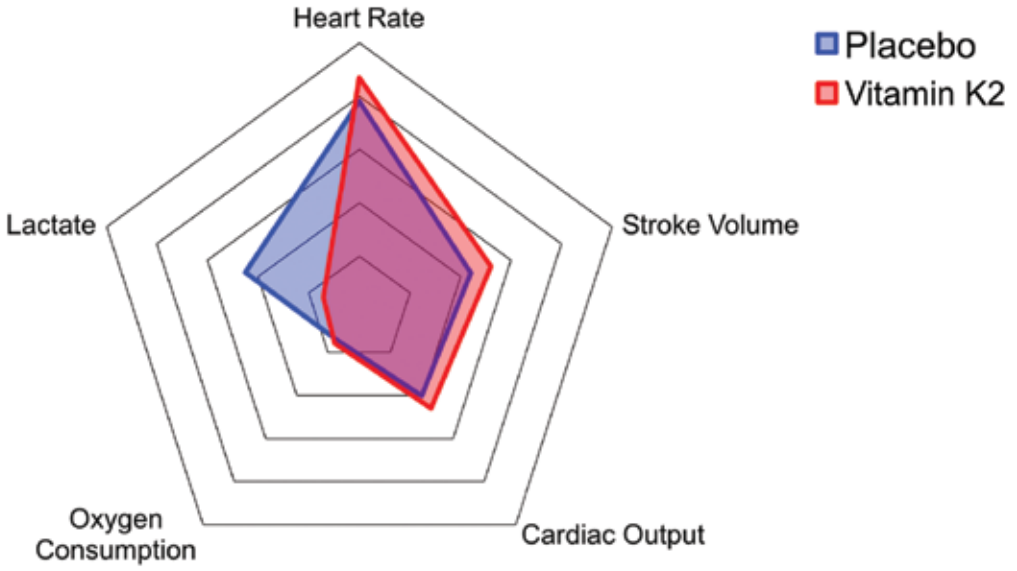
The AUC of the 2 treatment groups did not differ at baseline for any of the outcome variables. That finding means that the 2 groups, even with randomization, had balanced cardiovascular responses at baseline. Given the lack of a

Table 2. Variables for Mean Physiological Responses at Baseline and Postintervention

		Baseline					Postintervention				
Variable	**Group**	**Stage 1 Mean ± SE**	**Stage 2 Mean ± SE**	**Stage 3 Mean ± SE**	**Stage 4 Mean ± SE**	**Stage 5 Mean ± SE**	**Stage 1 Mean ± SE**	**Stage 2 Mean ± SE**	**Stage 3 Mean ± SE**	**Stage 4 Mean ± SE**	**Stage 5 Mean ± SE**
Heart rate, bpm	Control	125.4 ± 3.6	138.0 ± 3.7	152.4 ± 3.9	166.9 ± 5.6	175.4 ± 3.3	132.9 ± 4.0	141.8 ± 5.6	152.0 ± 5.3	166.4 ± 4.6	169.3 ± 3.3
	Intervention	129.9 ± 3.6	143.6 ± 3.7	154.8 ± 3.9	168.6 ± 5.6	180.8 ± 3.3	123.9 ± 4.0	138.0 ± 5.6	152.9 ± 5.3	167.6 ± 4.6	183.5 ± 3.2
Stroke volume, mL/beat	Control	80.9 ± 4.8	77.3 ± 6.4	78.6 ± 5.9	82.2 ± 6.2	88.7 ± 7.8	74.2 ± 5.1	82.7 ± 5.5	92.8 ± 6.4	95.1 ± 6.6	101.8 ± 7.6
	Intervention	73.8 ± 10.3	76.8 ± 10.0	76.6 ± 9.8	79.3 ± 9.2	75.2 ± 8.4	79.4 ± 10.6	78.2 ± 9.2	83.8 ± 9.6	84.6 ± 9.6	86.6 ± 9.6
Cardiac output, L/min	Control	10.2 ± 0.5	11.0 ± 0.6	12.8 ± 0.7	14.5 ± 0.9	15.8 ± 0.8	11.1 ± 0.6	12.0 ± 0.7	13.5 ± 0.6	14.5 ± 0.7	15.6 ± 0.8
	Intervention	10.8 ± 0.6	12.5 ± 0.5	13.9 ± 0.7	15.8 ± 0.7	16.9 ± 0.7	11.4 ± 0.9	13.1 ± 1.1	14.6 ± 1.1	16.5 ± 1.1	19.1 ± 1.2
Oxygen consumption, mL/kg/min	Control	20.8 ± 1.3	24.7 ± 2.1	29.6 ± 2.2	35.6 ± 3.0	42.7 ± 2.9	22.2 ± 4.4	26.9 ± 3.4	35.3 ± 2.4	40.5 ± 3.1	47.2 ± 2.5
	Intervention	22.4 ± 2.9	29.1 ± 3.0	32.9 ± 3.7	40.6 ± 3.7	46.4 ± 3.1	25.9 ± 3.2	30.4 ± 2.4	34.8 ± 2.7	42.2 ± 3.2	48.6 ± 4.4
Blood lactate, mmol/L	Control	3.2 ± 0.6	3.8 ± 0.7	5.4 ± 1.3	6.6 ± 1.2	10.7 ± 1.4	3.2 ± 0.6	4.9 ± 1.2	5.8 ± 1.3	7.9 ± 1.8	11.7 ± 1.7
	Intervention	3.06 ± 0.6	4.1 ± 0.7	4.9 ± 0.6	8.3 ± 0.9	11.9 ± 0.8	3.8 ± 0.7	3.8 ± 0.6	5.2 ± 1.0	7.8 ± 1.1	10.7 ± 1.3

Abbreviation: SE, standard error of mean.

Figure 3. To visualize the 5 outcome variables (heart rate, stroke volume, cardiac output, oxygen consumption, and blood lactate) on the same scale all data maximal response data after 8 wk of treatment with either a vitamin K_2 (red) or control (rice flour; blue) were normalized using a Log10 adjustment. Plotted values represent increments of a Log10 scale. consuming either a specific supplement. This figure demonstrates that vitamin K_2 treatment was associated with increased cardiac output, stroke volume, heart rate, and decreased blood lactate. Overall, these changes are consistent with increase maximal cardiovascular performance with oral vitamin K_2 supplementation.



difference at baseline, the research team's analysis focused on comparing the intervention group's response following 8 weeks of vitamin K_2, which is the red area in Figure 3, compared with the control group's response to the placebo, which is the blue area in Figure 3. Although the AUC responses did not reach statistical significance, the AUC for heart rate trended toward the intervention group having a 16% greater heart rate AUC than the control group ($P = .070$). No trends were observed for stroke volume, cardiac output, oxygen consumption, or blood lactate AUC.

DISCUSSION

Previous research has examined the ability of vitamin K_2 supplementation to reverse age-associated decreases in cardiovascular function or disease via restoration of production of mitochondrial ATP.[1-3,5,7,8,10] The present study sought to determine if previously described effects could translate to active individuals when combined with a regular training plan.

A common problem in individuals with a high degree of aerobic training is that they tend to experience decreases in maximal heart rate, which is a side effect of training-induced

expansion of blood volume.[13,14] Unfortunately, reduced maximal heart rate negatively influences the ability to maximize cardiac output. Thus, the current research team attempted to use vitamin K_2 supplementation to restore the heart-rate response in the presence of elevated blood volume.

In the present study, the research team found that consumption of a supplement containing vitamin K_2 was associated with a trend toward an increase in heart rate AUC, which may be the cause of the observed significant increase in maximal cardiac output that the study found. The effect size of the heart rate AUC (0.25) ended up being much lower than what the current research team observed in its pilot experiment compared to the effect size for maximal cardiac output (0.32), which was similar to what the team had anticipated.

A much lower effect size for heart rate AUC likely explains the lack of significance at the current sample size; however, with additional participants, that finding may translate into a significant outcome effect. Regardless of significance, the AUC analysis revealed that vitamin K_2 supplementation was associated with a cardiovascular profile characterized by increased cardiac output, increased heart rate, and decreased blood lactate compared to the placebo following 8 weeks of exercise training with the supplementation (Figure 3).

In particular, the current study's finding of a 12% increase in maximal cardiac output might translate into an effect on endurance exercise capacity. Without the vitamin K_2 supplement, training-induced changes in maximal cardiac output could take 6 to 9 months of continuous training to achieve. Supplementation with vitamin K_2 during training may reduce that training window by approximately 60%.

To the current research team's knowledge, the present study is the first to examine the potential of vitamin K_2 supplementation to increase the effectiveness of cardiovascular training. As with any study, the current study is not without limitations. For example, because the research team used a 2-month intervention, the study was unable to determine the time course of change associated with K_2 supplementation. In addition, it was not feasible to have the same participants complete both conditions (ie, to use a crossover design); the current model was used because it was unknown how long it can take K_2 to wash out of the system.

Care should be taken when interpreting the present findings because additional studies will be needed to validate the study's observations. The inclusion of the placebo group and its lack of change does help; however, more mechanistic work is likely needed, perhaps within an animal or cell culture model to measure changes in cardiac myocyte ATP production before and after supplementation/exposure to vitamin K_2.

The limitations described previously are not unique to vitamin K_2 supplementation but are common limitations of research involving either novel dietary supplements and/or novel applications of established supplements. Future research should seek to determine if similar benefits can be achieved during other forms of exercise with vitamin K_2 supplementation. In addition, given the current study's discovery of the novel effect of vitamin K_2 supplementation on cardiac output, additional exploration of other cardiovascular effects may be warranted.

CONCLUSIONS

Although vitamin K_2 supplementation has previously been reported to improve cardiovascular function in diseased patients, to the research team's knowledge, the current study is the first to report its potential in active individuals. More research is needed to fully evaluate the potential effect of the observed effects.

AUTHOR DISCLOSURE STATEMENT

The authors report no conflicts of interest with regard to the present study. The study was funded in part by a grant from Nu Science Trading to the University of North Texas (Denton, TX, USA). The authors received no direct financial support, and the funder had no role in the interpretation of the study's key findings.

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