Journal of the American Heart Association

ORIGINAL RESEARCH

Acute Effects of Cannabis Inhalation on Arterial Stiffness, Vascular Endothelial Function, and Cardiac Function

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BACKGROUND: The cardiovascular impact of cannabis use is incompletely understood. Although evidence links chronic use to an increased risk of disease and adverse cardiovascular events, few studies have investigated the acute effects of cannabis inhalation on subclinical dysfunction. Furthermore, it remains unknown how method of inhalation and cannabinoid profile modify risk. While controlling for inhalation method and the effects of either Δ-9-tetrahydrocannabinol (THC) or cannabidiol (CBD), we examined the acute cardiovascular effects of cannabis use on arterial stiffness, vascular endothelial responsiveness, and cardiac function, as markers of cardiovascular impairment.

METHODS AND RESULTS: Twenty-two young, healthy, cannabis users were assessed for arterial stiffness via pulse wave velocity, vascular endothelial function via brachial artery flow mediated dilation, and cardiac function via echocardiography, before and after (1) smoking THC-predominant cannabis (S-THC), (2) vaporizing THC-predominant THC (V-THC), and (3) vaporizing cannabidiol-predominant cannabis (V-CBD). S-THC and V-THC increased heart rate (S-THC: Δ17±15 bpm, V-THC: Δ16±16 bpm;both $P<0.0001$) and mean arterial pressure (S-THC: Δ7±6 mm Hg, V-THC: Δ5±5 mm Hg;both $P<0.0001$) whereas V-CBD did not (Δ1±4 bpm, Δ3±4 mm Hg;both $P>0.05$). After inhalation, pulse wave velocity increased (S-THC: Δ0.29±0.75 m/s, V-THC: Δ0.42±0.74 m/s, V-CBD: Δ0.10±0.44 m/s; $P=0.002$) and diastolic function was reduced ([early/late ratio] S-THC: Δ-0.2±0.53, V-THC: Δ-0.33±58, V-CBD: Δ0.01±66; $P=0.03$). Differences in heart rate were related to changes in pulse wave velocity ($r^2=0.2$; $P=0.0002$) and diastolic function ($r^2=0.26$; $P<0.0001$). Inhalation method did not alter these cannabinoid-dependent responses.

CONCLUSIONS: THC predominant, but not cannabidiol predominant, cannabis elicits increases in heart rate and blood pressure irrespective of inhalation method, which may increase arterial stiffness and reduce diastolic function. These findings implicate THC as a relevant factor for cannabis-related subclinical cardiovascular dysfunction.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT04693884.

Key Words: echocardiography ■ flow-mediated dilation ■ marijuana ■ smoking ■ vaporization

See Editorial by Ilonze and Page.

The United Nations Office on Drugs and Crime currently lists cannabis as the most widely used recreational drug in the world, with an estimated 218 million users.[1] Cannabis use is increasing in numerous regions of the world,[1–4] yet despite this widespread prevalence, how cannabis acutely affects the cardiovascular system remains poorly understood. This knowledge gap is of significant concern given emerging evidence to suggest that cannabis use may be associated with increased risk of cardiovascular

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This article was sent to Sula Mazimba, MD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

RESEARCH PERSPECTIVE

What Is New?

- We report the effects of different forms of cannabis use on pulse wave velocity, flow-mediated dilation, and echocardiographic outcomes, to determine whether use induces subclinical cardiovascular dysfunction; within this aim, we examined the degree to which predominant cannabinoid and inhalation method contribute to these effects.
- Inhalation of Δ-9-tetrahydrocannabinol-predominant cannabis increased heart rate and blood pressure independent of inhalation method, while arterial stiffness and cardiac function were generally increased by cannabis inhalation.

What Question Should Be Addressed Next?

- Subsequent work must identify the degree to which these acute effects contribute to the progression of cardiovascular disease in order to fully characterize the clinical risk profile of cannabis use.

Nonstandard Abbreviations and Acronyms

A	peak late diastolic transmitral filling velocity
E	peak early diastolic transmitral filling velocity
E'	peak early diastolic tissue velocity
FMD	flow-mediated dilation
PWV	pulse wave velocity
SR	shear rate
THC	Δ-9-tetrahydrocannabinol

disease including hypertension,[5,6] dysrhythmia,[7] heart failure,[8] myocardial infarction[9,10] and stroke.[11] This has prompted recognition by the American Heart Association of the urgent need for a greater understanding of the acute and chronic effects of cannabis use on the cardiovascular system.[12]

To understand links between cannabis use, cardiovascular events, and chronic cardiovascular disease, it is necessary to identify potential underlying pathophysiological mechanisms. Subclinical cardiovascular dysfunction both contributes to, and is predictive of, cardiovascular disease; thus, the effect of cannabis on such measures provides valuable insight into the process of disease development.[13–15] Arterial stiffening contributes to hypertension,[16] is independently related to cardiovascular events and mortality,[17,18] and has been shown to be elevated in habitual cannabis users.[19–21] The capacity of the vasculature to regulate its own diameter and blood flow is indicative of proper function, and accordingly, assessment of endothelial-dependent vasodilatory capacity holds prognostic value in both healthy and diseased populations.[22–24] Exposing rodents to cannabis smoke impairs conduit artery endothelial-dependent vasodilation; however, it is unknown whether this occurs in the human.[25,26] Habitual cannabis users present with lower left ventricular function compared with healthy, age-matched controls.[21,27] Outdated echocardiographic assessments of cardiac function demonstrate equivocal alterations following cannabis use,[28–31] whereas ex vivo data reveal cannabinoid receptor-mediated impairment to myocardial contractility.[32] However, no work exists examining the effects of cannabis using modern-day echocardiographic techniques, which have predictive value in the assessment of cardiovascular disease risk.[14,15]

Although these data portend a general relationship between cannabis use and both cardiovascular disease risk and impaired cardiac or vascular function that precedes disease development, they are largely limited to preclinical data, case reports, reviews, and population-based studies rather than prospective or interventional studies. Furthermore, existing work does not describe the range of effects that may exist given the wide variety of forms and means by which individuals can use cannabis. Although cannabis is stereotypically inhaled via smoking, novel "dry flower vaporizers" circumvent smoke exposure via aerosolization of cannabinoids and are marketed to minimize the detrimental effects to health. However, these claims remain untested with regard to the human cardiovascular system, and do not hold true in rodents.[26] Many commercially available cannabis products are devoid of the psychoactive cannabinoid Δ-9-tetrahydrocannabinol (THC), an agonist of cannabinoid receptor 1 (located in cardiovascular tissues[32,33]), and instead mostly contain the nonpsychotropic cannabinoid cannabidiol (CBD), which does not interact with cannabinoid receptor-1.[34] This is an important distinction, as the acute cardiovascular effects of THC are generally more pronounced than those of CBD.[35–41] Given these factors, an understanding of the effects of cannabis inhalation that may contribute to disease progression in cardiovascular tissues requires direct consideration and comparison of both method of inhalation and cannabinoid exposure.

The purpose of this study was to determine if cannabis inhalation causes subclinical cardiovascular dysfunction, indicated by physiological measures predictive of disease risk, while considering inhalation methods and specific cannabinoid exposure.

We hypothesized that THC-predominant cannabis would elicit tachycardia and hypertension, with associated arterial stiffness, while impairing endothelial-dependent vasodilation and cardiac function, whereas CBD-predominant cannabis would not. We further hypothesized that the cardiovascular effects of cannabis inhalation would be more pronounced when smoked compared with aerosolized in a vaporizer.

METHODS

Participants

Study participants were required to be free of chronic disease, be of legal age to purchase cannabis in Canada, and identify as a regular user who used inhaled cannabis at least once per week in the month before enrollment. Exclusion criteria were (1) current or past use of recreational substances other than cannabis (excluding alcohol), (2) cigarette smoking, (3) a personal or family history of psychosis, (4) mood or anxiety disorder, (5) systolic blood pressure ≥160 mm Hg, (6) diastolic blood pressure ≥90 mm Hg, (7) pregnant or planning to be pregnant, and (8) currently using prescription medication (exclusive of oral contraceptives). All participants provided written informed consent and this registered trial was approved by the institutional human research ethics board and Health Canada (NOL263414). This work is part of a larger registered clinical trial (clinicaltrials.gov, NCT04693884) and select hemodynamic data and other outcomes have been reported elsewhere.[37,42]

General Procedure

Participants attended four separate laboratory visits. The first visit (control) involved obtaining informed consent, collecting a urine sample to confirm prior drug use, and conducting baseline echocardiographic scans. The remaining 3 visits were experimental interventions during which cannabis was inhaled. Before all visits, participants abstained from cannabis use for ≥48 hours; exercise, alcohol, and vitamin use for ≥24 hours; caffeine for ≥12 hours; and calorie consumption for ≥6 hours.

At each visit, participants provided a urine sample to confirm abstention of recent (≥48 hours) cannabis use and other recreational substances (NarcoCheck, Montlucon, France). Participants rested supine on an echocardiographic examination table for 5 minutes before cardiovascular assessments. In the first visit, brachial blood pressure and heart rate were measured in triplicate using an automated oscillometric sphygmomanometer (BPTru Medical Devices, Coquitlam, Canada) and a baseline echocardiographic exam was completed. On subsequent visits, after initial measurements of brachial blood pressure and heart rate, carotid-femoral pulse wave velocity was measured via applanation tonometry as an indicator of arterial stiffness (AtCor Medical, Sydney, Australia). This was followed by assessment of vascular endothelial function via a brachial artery reactive hyperemia flow-mediated dilation (FMD) test. After inhaling cannabis, participants returned to the echocardiographic examination table for repeated measurements of brachial blood pressure, heart rate, arterial stiffness, and vascular endothelial function, as well as the same transthoracic echocardiographic exam completed during their control visit. The cannabis interventions and detailed assessments of arterial stiffness, vascular endothelial function, and cardiac function are described subsequently.

Cannabis

A custom-built inhalation chamber was used for cannabis administration. The chamber was equipped with negative pressure generation and a dual-filter system (carbon and HEPA), which enabled participants to inhale the provided cannabis without exposure to residual cannabis aerosol/smoke (see Cheung et al. 2024).[43] Cannabis was sourced from an accredited manufacturer and was analytically tested to confirm precise cannabinoid concentrations. Three cannabis conditions were studied. The inhalation methods were traditional smoking, using a metal pipe and ignition source, or using a dry-cannabis flower vaporizer (Storz and Bickel, Tuttlingen, Germany) set to 190 °C for aerosolization. One cannabis variant contained primarily THC (100 mg, 13.6% THC, <1% cannabidiol) and a second contained primarily cannabidiol (100 mg, 14.5% cannabidiol, <1% THC). Therefore, the 3 cannabis conditions were:

1. S-THC: smoking THC-predominant cannabis (100 mg, 13.6% THC, <1% cannabidiol).
2. V-THC: vaporizing THC-predominant cannabis (100 mg, 13.6% THC, <1% cannabidiol).
3. V-CBD: vaporizing cannabidiol-predominant cannabis (100 mg, <1% THC, 14.5% cannabidiol).

No protocol involving smoking of high cannabidiol cannabis was employed in the present study, as the a priori research questions were to assess the independent effects of inhalation method and cannabinoid composition within inhaled cannabis and not the interactive effects of these 2 factors.

Participants were instructed to follow a protocol involving a 5-second inhalation, followed by a 10-second hold, with 45-second in between inhalations. For safety and practicality, deviations from the protocol were permitted as necessary (eg, coughing or laughing) and no

set number of inhalations were required. Cannabis inhalation was completed within 10 minutes.

Pulse Wave Velocity

Arterial stiffness was estimated via the semiautomated measurement of carotid-femoral pulse wave velocity (PWV; AtCor Medical, Sydney, Australia). As per recommended procedures of the expert consensus,[44] peripheral pulse sites of the carotid and femoral arteries were identified and marked on the neck and femoral triangle, wherein a high fidelity tonometer was placed to measure the arrival of pulse waves. The distance between these sites and the sternal notch was measured and used to estimate the length of the aorta. Dividing the distance by the average time delay between central and peripheral pulse waves of 10 cardiac cycles produced a PWV value. The foot of peripheral pulse waveforms was determined using the intersecting tangent method and the mean of 3 measurements was taken to obtain a PWV for each time point. Measurements were discarded if the heart rate differed by >5 bpm, or the variation in pulse transit time exceeded 10%.

Flow-Mediated Dilation

We measured brachial artery vascular endothelial function using a standard reactive-hyperemia FMD test.[45] FMD tests were conducted in accordance with guideline recommendations (with the exception of the use of a stereotactic probe-holder) using ultrasound (Vivid-Q, General Electric; Boston) with a 6 to 13 MHz linear array transducer.[46] In the supine position, the right brachial artery was imaged using duplex ultrasound (insonation angle 60°) with simultaneous Doppler measurements of blood velocity across the span of the artery. After a 60-second baseline, a tourniquet cuff positioned 5 to 10 cm distal to the probe was inflated to 220 mm Hg for 5 minutes. Following cuff deflation, the hyperemic and vasodilatory effects were recorded for 3 minutes for offline analysis.

A single investigator, blinded to condition and time point, used continuous edge detection software (Quipu, Pisa, Italy) to analyze FMD tests. Arterial diameter and blood velocity were averaged into 3-second bins throughout the test and missing data were interpolated from adjacent time bins. Shear rate (SR) was used as a surrogate for shear stress exerted on the endothelium, which is accepted to be the primary stimulus for nitric oxide-mediated FMD.[47] SR was calculated in each time bin as 4 (mean blood velocity/arterial diameter). SR over a given period (ie, baseline, ischemia, recovery) was quantified by summating SR for each 3-second time bin and expressed as area under the curve (AUC). FMD was calculated as the change in vessel diameter in the recovery period (ie, post-schemia) relative to mean baseline diameter in the initial 60-second period. FMD was normalized to SR AUC for the 30-second postischemia, 60-second postischemia, and postischemia before the moment of peak vessel dilation.

Echocardiography

Cardiac function was measured using transthoracic echocardiography, performed with participants resting in the left lateral decubitus position. Images were captured from the parasternal long-axis view, parasternal short-axis view at the basal, midpapillary, and apical levels, and the apical 4-chamber view. Images were captured using a 1.5 to 3.6 MHz phased array transducer in accordance with recommendations from the American Society of Echocardiography.[48] Two-dimensional B-mode imaging and tissue Doppler imaging were captured and stored for offline analysis at a minimum frame rate of 50 fps and 100 fps, respectively, across 5 cardiac cycles.

Echocardiographic images were analyzed in a blinded fashion, using EchoPac Software (General Electric Healthcare, Boston, MA). Measurements were made on 3 cardiac cycles and expressed as the mean. Stroke volume and left-ventricular (LV) ejection fraction were determined using Simpson's method from apical 4-chamber images of LV chamber volumes.[49] Peak transmitral filling velocity was measured using Doppler sampling distal to the mitral valve where the valve leaflets did not enter the sample volume. Doppler measures at the level of the mitral annulus were used for peak myocardial tissue velocity. Peak transmitral filling velocity and tissue velocity during early (*E*, *E'*) and late (peak late diastolic transmitral filling velocity [*A*], peak late diastolic tissue velocity) diastole, and systole were identified in the spectral Doppler signal, with cardiac phase confirmed using lead-II ECG. Diastolic function was evaluated using the *E/A* ratio and the *E/E'* ratio. Left atrial (LA), right atrial (RA), and RV size were quantified by tracing the endocardial border of the respective chamber either at the end of ventricular systole (LA/RA) or end-diastole (RV). RV fractional area change was determined by dividing the difference between RV end-diastolic area and RV end-systolic area by RV end-diastolic area. Ventricular elastance was calculated by dividing estimated end-systolic pressure (derived by multiplying brachial artery systolic blood pressure by 0.9)[50] by end-systolic volume, and arterial elastance by dividing end-systolic pressure by stroke volume. Arterio-ventricular coupling was assessed using the ratio of arterial elastance and ventricular elastance. Tricuspid annular plane systolic excursion was measured using M-mode in the apical 4-chamber view.

Speckle tracking was used to analyze LV deformation during both systole and diastole. Twist was calculated by subtracting peak basal rotation from peak

apical rotation, wherein rotation in the counterclockwise direction was positive and rotation in the clockwise direction was negative. Peak longitudinal strain was captured from apical-4 chamber images, whereas peak circumferential and radial strain were captured from parasternal short-axis images at the midpapillary level. Using 6 individual myocardial wall segments, strain and rotation parameters were calculated across 3 cardiac cycles. If an individual wall segment was inadequately tracked, the segment was excluded for that particular cardiac cycle.

Statistical Analysis

Experimental conditions were compared using linear mixed models. For comparison of hemodynamic data and vascular outcomes (ie, related to PWV or FMD) time (pre versus post) and condition were incorporated into the model as fixed factors, with participants included as a random factor. Given that cardiac scans do not contain a within-day control, only condition was included as a fixed factor. When appropriate, post hoc tests with Šidák corrections were conducted to assess differences between conditions and time points within conditions. Pearson bivariate correlations were used to examine the relationship between blood pressure or heart rate and other variables. An a priori power analysis indicated that 15 participants were required to achieve a statistical power of 0.8 at our selected alpha level of $P \leq 0.05$, considering anticipated changes in endothelial function (ΔFMD: 2%±1%) and arterial stiffness (ΔPWV: 1.5±0.5 m/s). Additional participants were included to mitigate the risk of attrition. Statistical analyses were performed using Prism 9 (GraphPad, Boston, MA). Data are presented as mean±SD.

RESULTS

Participants

Twenty-two ostensibly healthy cannabis users with a body mass index between 18 and 30 kg/m^2 were included in the study (Table 1). Male and female sex were equally represented, with weekly instance of cannabis use ranging from <1 to >7 times; however, the majority reported 1 or 2 instances per week. Owing to poor image quality in at least 1 time point, 6 participants' FMD data were excluded, leaving a subset of 16 participants for this measure.

Hemodynamics

Cannabis inhalation altered both blood pressure and heart rate in a cannabinoid-dependent manner (Figure 1). Diastolic blood pressure (S-THC: Δ6±6 mm Hg, V-THC: Δ5±5 mm Hg, V-CBD: Δ2±4 mm Hg), mean arterial pressure (S-THC: Δ7±6 mm Hg, V-THC: Δ5±5 mm Hg, V-CBD: Δ3±4 mm Hg), and heart rate (S-THC: Δ17±15 bpm, V-THC: Δ16±16 bpm, V-CBD: Δ1±4 bpm) were increased in both THC conditions (all $P<0.001$) but not in the CBD condition (all $P>0.05$). Although the pooled data demonstrated a general increase in systolic blood pressure ($P<0.0001$) with cannabis inhalation, the increases in S-THC (Δ7±7 mm Hg; $P<0.0001$) and V-THC (4±6 mm Hg; $P=0.03$) were significant, whereas the increase in V-CBD only neared significance (3±5 mm Hg; $P=0.051$).

Table 1. Characteristics of the 22 Individuals Who Completed the Study

	No.=22
Demographics	
Sex (male/female)	11/11
Age, y	22.4±3.3
Height, m	1.72±0.06
Weight, kg	73.6±9.6
Body mass index, kg/m^2	24.8±2.6
Average cannabis use (sessions/week)	
<1	2
1–2	14
3–4	2
5–6	2
>7	2

All participants were habitual cannabis users who reported using cannabis at least once per week for the month before enrolling in the study, of legal age to purchase cannabis in Canada, and were ostensibly healthy. Data are presented as mean±SD.

Arterial Stiffness

There was a general increase in PWV following all cannabis conditions (Figure 2A through 2C). The magnitude of these increases were +Δ0.29±0.75 m/s for S-THC, +Δ0.42±0.74 m/s for V-THC, and +Δ0.10±0.44 m/s for V-CBD. Changes in PWV were weakly correlated with changes in systolic blood pressure ($r^2=0.09$, $P=0.02$), diastolic blood pressure ($r^2=0.10$, $P=0.01$), and heart rate ($r^2=0.20$, $P=0.0002$; Figure 2D).

Endothelial Function

None of the cannabis inhalation conditions resulted in changes to FMD as a percentage of baseline diameter (Table 2). SR AUC, in the first 30 seconds and 60 seconds of the hyperemic period was similar in each condition. Additionally, the SR AUC preceding the time of vessel dilation (ie, peak FMD) was similar at all time points. When FMD was normalized to 30 seconds SR AUC, 60 seconds SR AUC, and the SR AUC preceding the peak FMD, there were still no effects of cannabis inhalation. There was a reduction in baseline artery diameter after cannabis inhalation.

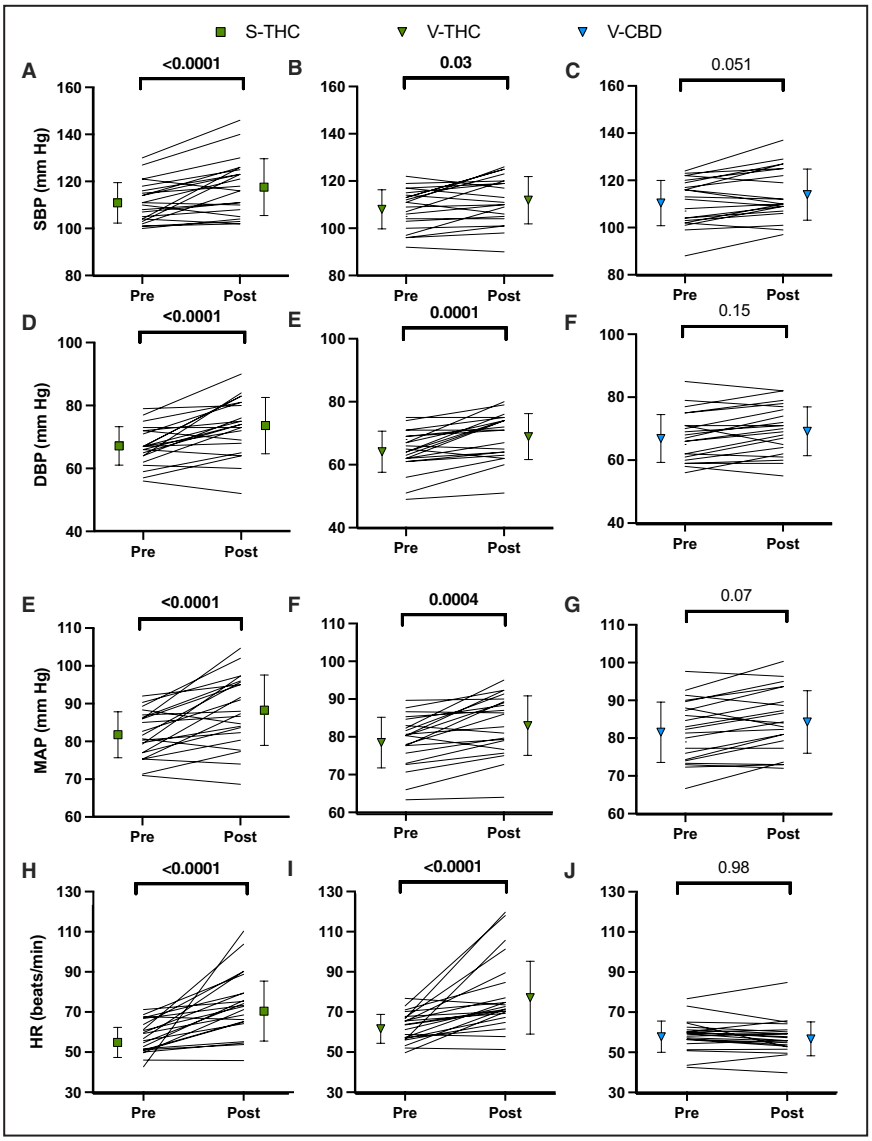

Figure 1. Systolic blood pressure (A through C), diastolic blood pressure (D through F), mean arterial pressure (E through G), and heart rate (H through J) following inhalation of THC-predominant cannabis via either S-THC or V-THC, or V-CBD.

All of SBP, DBP, MAP, and HR were increased in S-THC and V-THC, but not in V-CBD, suggesting the hemodynamic effects of cannabis are dependent upon the presence of THC. Symbols represent means. Error bars represent SDs. Solid lines represent individual responses. DBP indicates diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure; S-THC, smoking THC-predominant cannabis; THC, Δ-9-tetrahydrocannabinol; V-CBD, vaporizing cannabidiol-predominant cannabis; and V-THC, vaporizing THC-predominant cannabis.

Cardiac Function

There were minimal differences in systolic function between cannabis and control conditions (Table 3; Figure 3). Whereas peak septal and RV free wall peak systolic tissue velocity were similar between conditions, LV free wall S′ was elevated in V-THC compared with V-CBD. All other measures of systolic function, including end-systolic volume, ventricular elastance, arterioventricular coupling, stroke volume, LV ejection fraction, and RV fractional area change were similar across conditions. In support of unchanged systolic function, there were no differences in peak LV longitudinal, circumferential, or radial strain, nor were there differences in peak LV twist, systolic twist velocity, basal rotation, or apical rotation (Figure 4A through 4G). In contrast to systolic function, septal *A′*, *A*, and *E/A* ratio (Figure 5A through 5C) differed between conditions.

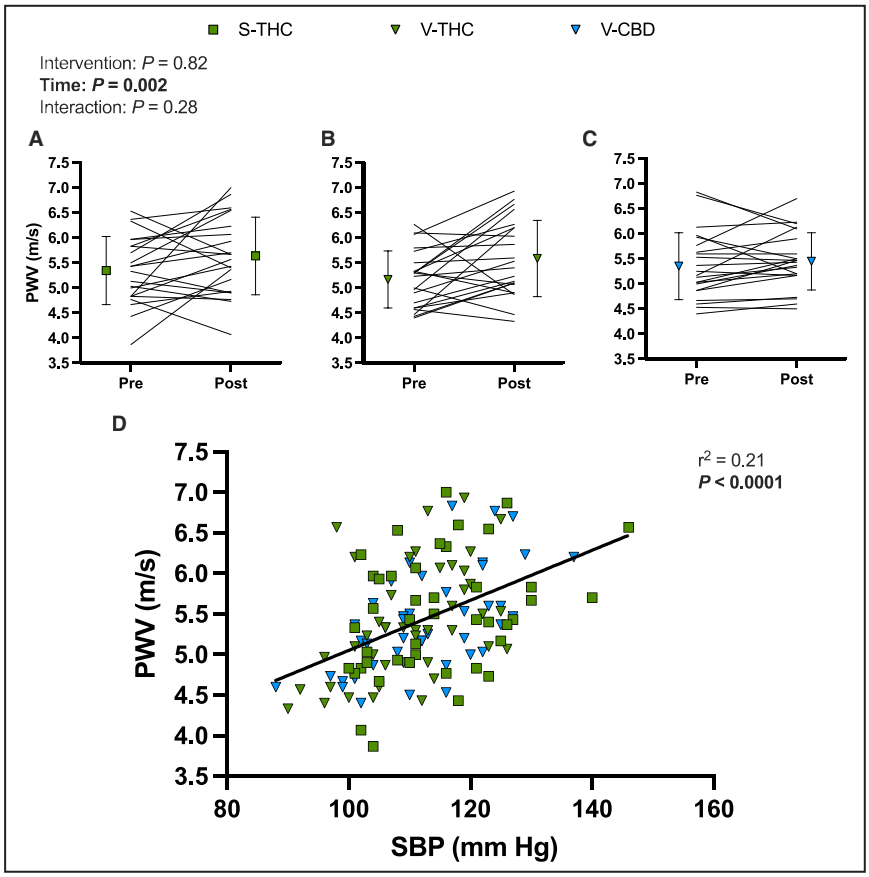

Figure 2. Pulse wave velocity following inhalation of THC-predominant cannabis via either S-THC (A) or V-THC (B), or V-CBD (C).
A main effect of time was observed, suggesting that cannabis inhalation increases PWV independent of whether it is smoked or vaporized, and whether it predominantly contains THC or cannabidiol. The relationship between change in HR and change in PWV (**D**) suggest that the effects of cannabis inhalation on PWV are associated with concomitant changes in HR. Symbols represent means. Error bars represent SDs. Solid lines represent individual responses. PWV indicates pulse wave velocity; S-THC, smoking THC-predominant cannabis; THC, Δ-9-tetrahydrocannabinol; V-CBD, vaporizing cannabidiol-predominant cannabis; and V-THC, vaporizing THC-predominant cannabis.

Although post hoc tests were not significant, it was generally observed that each of these measures of diastolic function were impaired in S-THC and V-THC compared with V-CBD. However, both *A* and *E/A* ratio were associated with heart rate (Figure 5D/E) and other measures of diastolic function (ie, septal *E′*, LV free wall *E′*, RV free wall *E′*, LV free wall peak late diastolic tissue velocity, RV free wall peak late diastolic tissue velocity, *E*, *E*:*E′*, and LV end-diastolic volume) were similar across all conditions (Table 3). Peak LV untwisting velocity was similar between all conditions (Figure 4H).

DISCUSSION

This study examined the extent to which cannabis inhalation elicits cardiovascular dysfunction and whether the inhalation method or specific cannabinoid exposure modified this effect, with the aim of understanding how cannabis potentially contributes to the progression of cardiovascular disease. The main findings were that THC-predominant but not CBD-predominant cannabis induced tachycardia and hypertension and that cannabis inhalation generally increases arterial stiffness, does not affect vascular endothelial function, and alters diastolic but not systolic cardiac function. Noted changes in function were generally related to elevations in heart rate and blood pressure, which, as mentioned, occurred only when THC-predominant cannabis was inhaled and not CBD-predominant cannabis. Furthermore, inhaling aerosolized cannabis via vaporization instead of smoking did not modify the cardiovascular impact of the drug. This underscores the importance of THC in cannabis driven changes in vascular and cardiac function. These findings provide

Table 2. Indices of Vascular Endothelial Function in a Subset of 16 Participants With Complete Data, Evaluated Through a Reactive Hyperemia Brachial Artery Flow-Mediated Dilation Test

	S-THC		V-THC		V-CBD		*P* value		
	Pre	Post	Pre	Post	Pre	Post	Time	Group	Interaction
Baseline artery diameter, mm	3.9±0.6	3.8±0.6	4.0±0.6	3.8±0.7	3.9±0.6	3.9±0.6	<0.0001*	0.9	0.08
30s shear rate AUC	3600±1434	3648±1599	3464±1071	3648±1009	3195±928	3348±823	0.9	0.7	0.5
60s shear rate AUC	5452±2176	5418±2688	5290±1633	4892±1614	4823±1391	4916±1198	0.6	0.6	0.6
Time to peak diameter shear rate AUC	5189±2241	5132±2190	5438±2310	4914±1849	4319±1436	5236±2240	0.7	0.97	0.08
FMD (%)	7.9±3.4	7.7±3.6	7.0±3.3	8.8±4.8	7.7±4.0	8.2±4.8	0.4	0.99	0.5
nFMD (%) 30s shear rate AUC	2.4±1.2	2.5±1.4	2.1±0.9	2.6±0.9	2.4±1.1	2.4±1.5	0.4	0.97	0.6
nFMD (%) 60s shear rate AUC	1.6±0.7	1.7±0.9	1.4±0.6	1.8±0.7	1.6±0.8	1.6±0.8	0.3	0.99	0.5
nFMD (%) Time to peak diameter shear rate AUC	1.8±1.0	1.7±0.1.0	1.5±1.0	1.8±0.7	1.8±0.8	1.6±0.8	0.97	0.91	0.3

FMD tests were performed before and after inhalation of inhalation of THC-predominant cannabis via either S-THC or V-THC, or V-CBD. Data are presented as mean±SD. AUC indicates area under the curve; FMD, flow-mediated dilation; nFMD, normalized flow-mediated dilation; S-THC, smoking THC-predominant cannabis; THC, Δ-9-tetrahydrocannabinol; V-CBD, vaporizing cannabidiol-predominant cannabis; and V-THC, vaporizing THC-predominant cannabis.

*Indicates significance.

insight into the acute effects of cannabis use, and future investigations should extend beyond young healthy cannabis users to fully determine the clinical relevancy of these effects.

Multiple reports suggest cannabis use increases the risk of myocardial infarction.[9,51–53] However, causality and the underlying mechanisms explaining this relationship remain to be firmly established. In the present study, we demonstrate substantial increases in heart rate (~Δ15 bpm) and blood pressure (~Δ5 mm Hg), and a more modest increase in arterial stiffness after inhalation of THC-predominant cannabis, regardless of inhalation method. Notably, the rise in PWV observed following THC use, although small, was of similar magnitude to that reported following cigarette use (both ~Δ0.5 m/s)[54] but was not specifically driven by the inhalation of combusted material. Given that the elastic (Windkessel) properties of the aorta are essential for dampening central systolic blood pressure, elevations in aortic stiffness following THC use may contribute to the associated hypertensive response, and consequently increase the risk of a cardiovascular event via increased afterload and myocardial work. This rapid rise in PWV should also be considered in the context of habitual cannabis users, who may already demonstrate elevated arterial stiffness at baseline,[19–21] and data that suggest that even small increases in PWV are clinically relevant, as each 1 m/s increase in PWV equates to a 14% increase in risk for all cardiovascular events.[17] Recently, our group identified a reduction in sympathetic outflow targeted to skeletal muscle vasculature after cannabis inhalation[42]; an effect likely mediated by the baroreflex, which we hypothesize exists to counter the hypertensive response to THC. In lieu of such a baroreflex-mediated reduction in vasoconstriction, the hypothetical augmentation of blood pressure, combined with small increases in arterial stiffness, could provide a mechanistic explanation for the associations between cardiac or cerebrovascular events and cannabis use.[8–11] Should this be the case, cannabis use in populations with an impaired baroreflex, such as those with cardiovascular disease or the healthy elderly, could face greater clinical risk. However, it is important to note that we observed a significant relationship between changes in PWV and changes in heart rate and blood pressure, which limits interpretation as to whether stiffness is secondary to tachycardic/hypertensive effects of THC or vice versa. Importantly, these associations were weak (r^2=0.09–0.2) and, thus, only a portion of the variance in this response is explained by hemodynamic changes. Collectively, these findings suggest that aortic stiffening, likely specific to THC, is

Table 3. Indices of Cardiac Function Assessed by Echocardiography Under Control Conditions or Following Inhalation of Inhalation of THC-Predominant Cannabis via Either S-THC or V-THC, or V-CBD

	Control	S-THC	V-THC	V-CBD	*P* value
LV systolic function					
Septal *S′*, cm/s	7.7±1.0	7.5±1.3	8.1±1.4	8.1±3.0	0.5
Free wall *S′*, cm/s	10.0±1.7	10.0±1.8	10.1±0.17[†]	9.5±1.6[#]	0.02[§]
End-systolic volume, mL	53±14	50±14	48±13	51±11	0.1
Arterial elastance, mm Hg/mL	1.59±0.29	1.6±0.42	1.57±0.39	1.50±0.21	0.2
Ventricular elastance, mm Hg/L	2.05±0.46	2.27±0.58	2.23±0.47	2.09±0.38	0.06
Vascular-ventricular coupling	0.81±0.15	0.75±0.16	0.73±0.14	0.74±0.12	0.1
Cardiac output, L/min	4.01±0.90	4.65±1.40	4.49±1.22	4.03±0.95	0.02[§]
LV diastolic function					
Septal *E′*, cm/s	12.1±2.4	11.9±1.9	11.6±2.4	12.3±1.8	0.6
Free wall *E′*, cm/s	16.4±2.6	16.2±3.2	16.8±2.9	16.6±1.9	0.8
Free wall *A′*, cm/s	6.1±1.9	6.4±1.7	6.1±2.0	5.7±1.7	0.4
E, m/s	0.81±0.12	0.86±0.15	0.81±0.10	0.82±0.10	0.2
E/*E′*	5.8±1.1	6.4±1.4	5.9±1.1	5.8±1.0	0.1
End-diastolic volume, mL	120±24	120±27	115±25	122±20	0.2
RV function					
E', cm/s	12.3±2.7	13.3±2.8	12.9±2.7	13.7±2.1	0.1
A', cm/s	8.9±2.3	10.3±2.9	9.0±1.9	9.0±2.1	0.09
S', cm/s	11.8±1.3	12.7±2.1	11.9±1.9	12.0±2.0	0.3
End-diastolic area, cm^2	20.6±3.4	20.0±3.3	19.6±3.8	20.2±3.6	0.2
End-systolic area, cm^2	11.0±2.4	10.5±2.3	10.5±2.6	11.2±2.3	0.08
Tricuspid annular plane systolic excursion, cm	2.5±0.5	2.5±0.2	2.5±0.4	2.5±0.4	0.96

Data are presented as mean±SD. *A*' indicates peak late diastolic tissue velocity; *E*, peak early diastolic transmitral filling velocity; *E*', peak early diastolic tissue velocity; LV, left ventricular; *S*', peak systolic tissue velocity; S-THC, smoking THC-predominant cannabis; THC, Δ-9-tetrahydrocannabinol; V-CBD, vaporizing cannabidiol-predominant cannabis; and V-THC, vaporizing THC-predominant cannabis.

[#]*P*<0.05 vs V-THC.

[†]*P*<0.05 vs V-CBD.

[§]Indicates significant fixed effect of condition.

an acute cardiovascular effect of cannabis and may increase the risk of acute cardiovascular events.

Although cannabis inhalation affected the central vasculature and hemodynamics, we observed no effect of cannabis on peripheral vascular endothelial function. This was counter to our hypothesis that cannabis inhalation would impair FMD, which was based on evidence that cannabis inhalation acutely impairs endothelial function in a rodent model[25,26] and that acute cigarette use impairs FMD in humans.[55] The discrepancy in FMD responses between animal and human models may be explained simply by differences in cannabis dose relative to organism size, as human and rat experiments have used similar absolute doses of cannabis.[25,26] Nevertheless, disentangling the equivocal findings surrounding the effects of cannabis on peripheral endothelial function[21,56] remains an important step in confirming a causal relationship between regular cannabis use, subclinical cardiovascular dysfunction, and the development of cardiovascular disease. In particular, this knowledge gap is essential for parsing contrasting evidence linking cannabis use to coronary artery disease,[57,58] given the relationship between risk and endothelial function.[45,59]

In contrast to previous work demonstrating reduced ejection time, stroke volume, ejection fraction, and end-diastolic volume after cannabis inhalation,[28–31] we saw minimal differences in systolic function after cannabis use. This contrasts previous work[28–31] and preclinical data[32] demonstrating impaired measures of systolic function or contractility with cannabinoid receptor-1 activation. Increased cannabinoid receptor-1-mediated beta-adrenergic activation of the heart and the resulting tachycardia associated with cannabis inhalation may compensate for intrinsic impairments in myocardial systolic function.[37,42,60,61] However, assessing this possibility is beyond the scope of this investigation. Our findings suggest that, at least in healthy young cannabis users, impairments to systolic function do not contribute to the elevated risk of acute cardiovascular events associated with cannabis use. In contrast to systolic outcomes, the only diastolic outcomes

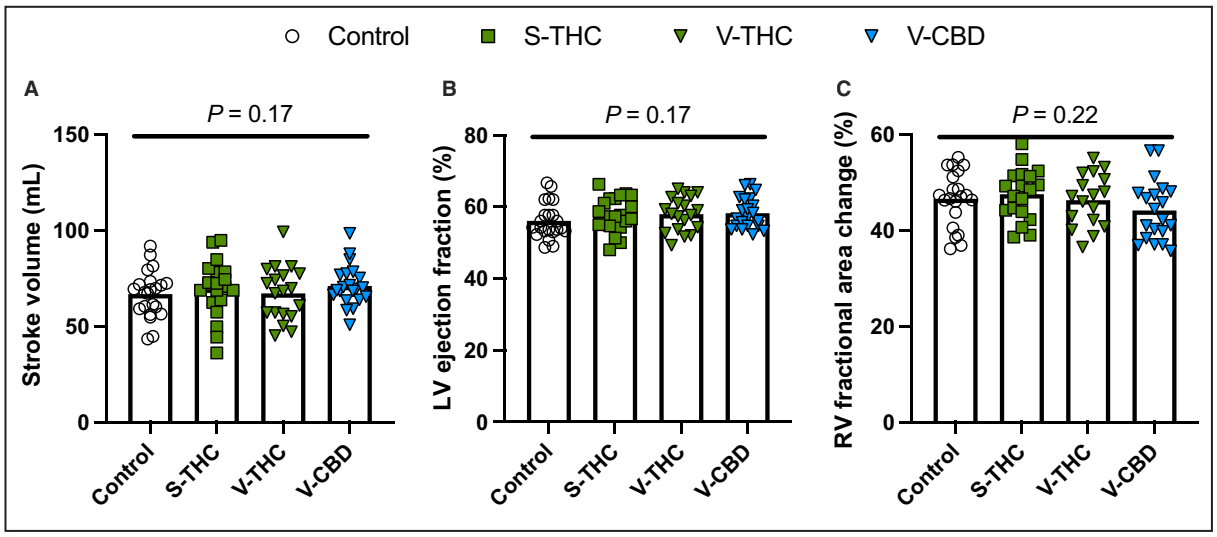

Figure 3. Indices of left ventricular (A/B) and right ventricular (C) systolic function under control conditions and following inhalation of THC-predominant cannabis via either S-THC or V-THC, or V-CBD.
None of stroke volume, LV ejection fraction, or RV fractional area change differed between control, and any cannabis inhalation condition, suggesting no effect of cannabis inhalation on cardiac systolic function. Bars represent means and symbols represent individual values. LV indicates left ventricular; RV, right ventricular; S-THC, smoking THC-predominant cannabis; THC, Δ-9-tetrahydrocannabinol; V-CBD, vaporizing cannabidiol-predominant cannabis; and V-THC, vaporizing THC-predominant cannabis.

affected in our study are known to be strongly influenced by heart rate,[62] which was acutely increased by THC inhalation but not by CBD inhalation. Specifically, we observed modest changes to *A*, peak late diastolic tissue velocity, and the *E/A* ratio, after inhalation of THC-predominant cannabis (*A*: ~Δ0.2 m/s; *E/A* ratio:

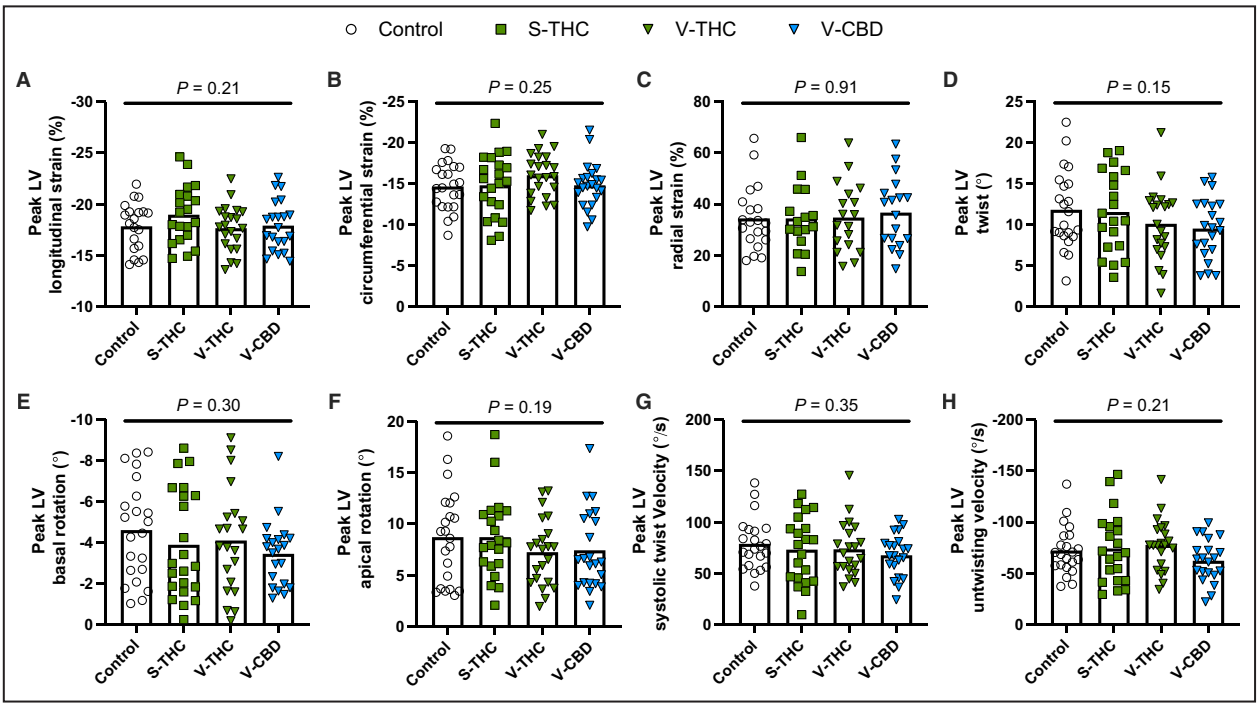

Figure 4. Peak left ventricular strain (A through C), twist (D), rotation (E/F), and twist velocities (G/H) under control conditions and following inhalation of THC-predominant cannabis via either S-THC or V-THC, or V-CBD.
None of the cannabis inhalation conditions altered these measures of LV mechanics from control conditions. Bars represent means and symbols represent individual values. LV indicates left ventricular; S-THC, smoking THC-predominant cannabis; THC, Δ-9-tetrahydrocannabinol; V-CBD, vaporizing cannabidiol-predominant cannabis; and V-THC, vaporizing THC-predominant cannabis.

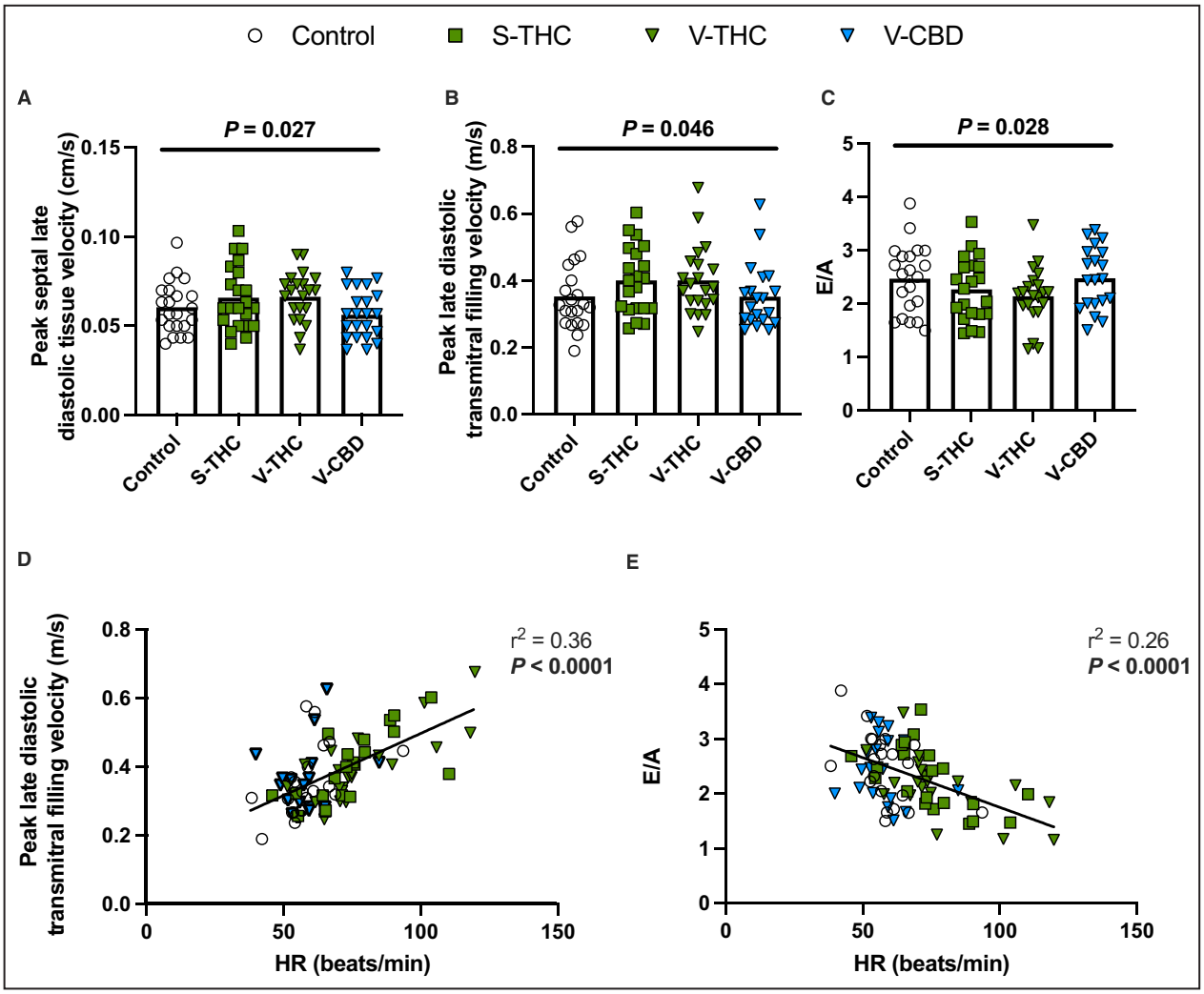

Figure 5. Indices of left ventricular diastolic function under control conditions and following inhalation of THC-predominant cannabis via either S-THC or V-THC, V-CBD.

Šidák corrected post hoc tests showed no differences in peak septal late diastolic tissue velocity (**A**), peak late diastolic transmitral filling velocity (**B**), and the ratio of peak early to peak late diastolic transmitral filling velocities (**C**) or between control and any cannabis inhalation conditions. The relationship between indices of diastolic function and heart rate (**D**/**E**) suggest that decrements in diastolic function following cannabis inhalation are associated with concomitant increases in heart rate. Bars represent means and symbols represent individual values. E/A indicates early/late; HR, heart rate; S-THC, smoking THC-predominant cannabis; THC, Δ-9-tetrahydrocannabinol; V-CBD, vaporizing cannabidiol-predominant cannabis; and V-THC, vaporizing THC-predominant cannabis.

~Δ-0.1–0.2) but not CBD-predominant cannabis. In line with our findings regarding arterial stiffness, this supports the general concept that acute cardiac- or vascular-specific effects of cannabis inhalation are likely influenced by the tachycardic effects of THC. The findings of Kanakis and colleagues also support this, demonstrating that altered cardiac function following cannabis use can be attenuated by preventing tachycardic and pressor effects with an autonomic blockade.[31,63] The results of our echocardiographic experiments align with our vascular findings in that there remains a gap to bridge between the reported chronic cardiovascular effects of cannabis use[19–21,27] and the observed acute effects on the same outcomes.

An aim of this study was to evaluate how the inhalation method and the relative doses of THC or CBD influence the acute cardiovascular effects of cannabis. Within this aim, we chose to study products representative of what is available to the North American recreational cannabis user, so that findings might be ecologically valid, informative to clinical practice, and widely generalizable. With regard to method of inhalation, we observed consistent effects of THC-predominant cannabis when it was combusted and inhaled as smoke compared with when it was heated and aerosolized. Given that our cannabis dose was chosen to mimic what a somewhat typical dose a recreational cannabis user might consume (ie, 100 mg of dry flower, ~10%–15% THC/

CBD), it appears that the effect of aerosolized THC-predominant cannabis inhalation is similar to that of cannabis smoke inhalation under real-world conditions and that the combustion of the many other molecules contained within cannabis contribute little to the cardiovascular response it elicits. It should be noted, however, that the inhalation of combusted material could be a detriment to the many other aspects of physical health. With regard to cannabinoids, when cannabis contained primarily CBD and little to no THC, the effects were minimal, with no increase in heart rate or blood pressure. However, it is important to note that vaporizers may be more effective at cannabinoid delivery as compared with traditional smoking, in that vaporized cannabis has been demonstrated to cause qualitatively stronger drug effects and both quicker onset and greater peak blood THC concentrations than an equivalent dose of smoked cannabis.[64] Nevertheless, our results suggest that, ecologically, the method of inhalation does not modify the cardiovascular effects of cannabis, whereas the presence of THC, but not CBD, appears to be more influential. These nuances must be considered by clinicians in practice, given the growing prevalence of recreational cannabis use in society.

Limitations

This study has limitations that should be considered. Due to the extensive testing and its context within a larger clinical trial, the sample size was constrained. Despite recruiting sufficient participants to detect an approximately 2% reduction in FMD and a 1.5 m/s difference in PWV, significant main effects and interactions were observed without significant post hoc comparisons, likely due to smaller than expected effects of cannabis and response variability. Thus, although this study provides important insight and a stepping-off point to consider the cardiovascular implications of the acute physiological effect of cannabis use, larger sample sizes in future studies may provide more definitive results. Additionally, the sample consisted of young, ostensibly healthy, habitual cannabis users and not those with cardiovascular disease, comorbidities, or elevated risk such as the elderly, which should be considered before generalizing our findings. Instead, the results offer fundamental insights into the acute cardiovascular effects of cannabis inhalation, its potential role in disease progression, and the impact of different cannabinoids and inhalation methods. Future work must be explore the effects of cannabis in higher risk populations to fully characterize the clinical risk associated with use.

CONCLUSIONS

Cannabis use is highly prevalent in many societies, and cardiovascular disease remains the leading cause of death globally.[65] It is currently unclear if and how cannabis might induce cardiovascular dysfunction and whether these effects represent pathophysiological mechanisms of disease development. By examining cannabis products representative of those available to the recreational consumer, our findings highlight (1) tachycardic and hypertensive effects of THC-predominant cannabis regardless of inhalation method, and not CBD-predominant cannabis; (2) a general effect of cannabis inhalation to increase arterial stiffness; (3) minimal changes to vascular endothelial function; (4) no changes to cardiac systolic function; and (5) modest changes to cardiac diastolic function, likely mediated by THC-associated tachycardia and not inhalation method. Although speculative, these effects could contribute to the progression of cardiovascular disease with repeated exposure. Future work is needed to determine whether this response is preserved in higher risk populations, such as the healthy elderly or those with cardiovascular disease, in order to better inform researchers and clinicians on the cardiovascular consequences of cannabis inhalation.

ARTICLE INFORMATION

Received July 15, 2024; accepted September 11, 2024.

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Sources of Funding

This work was supported by Mitacs and the Natural Sciences and Engineering Research Council of Canada.

Disclosures

None.

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