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Title: Case Report- Unstable Angina, Coronary Artery Disease, and Cannabis

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Abstract:

Rationale:

First discovered in 1990, the endocannabinoid system (ECS) was initially shown to have an intimate relationship with central areas of the nervous system associated with pain, reward, and motivation. Recently, however, the ECS has been extensively implicated in the cardiovascular system with contractility, heart rate, blood pressure, and vasodilation. Emerging data demonstrates modulation of the ECS plays an essential role in cardio metabolic risk, atherosclerosis, and can even limit damage to cardiomyocytes during ischemic events.

Patient Concerns:

This case describes a 63-year-old male who presented to a primary care physician for a medical cannabis (MC) consult due to unstable angina (UA) not relieved by morphine or cardiac medications; having failed all first- and second-line poly-pharmaceutical therapies. The patient reported frequent, unprovoked, angina and exertional dyspnea.

Diagnosis:

Having a complex cardiac history, the patient first presented 22 years ago after a suspected myocardial infarction (MI). He re-presented in 2010 and underwent stent placement at that time for inoperable triple-vessel coronary artery disease (CAD) which was identified via percutaneous transluminal coronary angioplasty. UA developed on

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follow up and, despite medical management over the past 6 years, his UA became progressively debilitating.

Interventions and Outcomes:

In conjunction with his standard cardiac care, patient had a gradual lessening of UA related pain, including frequency and character, after using an edible form of medical cannabis (MC) (1:1 CBD:THC). Following continued treatment, he ceased long term morphine treatment and describes the pain as no longer crippling. As demonstrated by his exercise tolerance tests, the patient experienced an improved functional capacity and reported an increase in his daily functioning, and overall activity.

Lessons:

This case uniquely highlights MC in possibly reducing the character, quality, and frequency of UA; while concordantly improving functional cardiac capacity in a patient with CAD. Additional case reports are necessary to verify this.

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Introduction:

Upon consumption, cannabis rapidly stimulates the endocannabinoid system (ECS) with an onset 20 mins to 2 hrs. after ingestion or from 2-20 mins after inhalation. The ECS consists of the neurotransmitters Anandamide (AEA) and 2-Arachidonoylglycerol (2-AG), the CB_1 and CB_2 receptor system, as well as other non-cannabinoid targets (GPCRs) [1]. The CB_1 receptor is most concentrated in the hippocampus, periaqueductal grey, spinal trigeminal nucleus, amygdala, cerebellum, basal ganglia [2], as well as cardiomyocytes where they promote negative inotrope and vasodilation [3, 4]. The CB_2 receptor system is largely concentrated outside of the CNS and primarily exhibits its effects on the immune system, systemic inflammatory state, the gut, cardiomyocytes, and vascular smooth muscle [3].

The physiological response to ingestion or inhalation of cannabis in an acute setting is well defined and consists of hypertension and reflex tachycardia [3, 4]. Whereas, in long-term users, or under chronic administration, cannabis produces bradycardia and hypotension [4]. It is largely believed that these physiological effects are controlled by a fluctuating excitation/inhibition of CB_1 receptors on post-synaptic sympathetic and parasympathetic fibers, during acute and chronic administration, respectively [2, 4]. Cannabis has also been shown to have significant properties as a vasodilator, acting through non-cannabinoid targets, such as the newly discovered GPCRs class known as the Transient Receptor Potential cation channel subfamily V member 1 (TRPV1) [1]. These effects are seen within minutes to hours of administration and mediated by the ECS; playing an essential role in cardio metabolic risk, atherosclerosis, and limiting damage to cardiomyocytes during ischemic events [3].

 doi:10.20944/preprints202011.0668.v1

Case presentation:

This case describes a 63-year-old male, former narcotics officer, with a complex cardiac history who first presented 22 years ago after a suspected myocardial infarction (MI). He has a 21-pack year history of smoking, but stopped immediately after his MI. In 2009, the patient re-presented to cardiology and underwent a nuclear stress test demonstrating moderate ischemia in the anterior and anterolateral walls. A subsequent angiogram showed significant calcification in the left main coronary artery (LMCA) and the proximal left anterior descending artery (LAD). Disease in the right main coronary artery (RMCA) was also noted. He was referred for a 2D echocardiogram (ECHO) and re-catheterization to explore the extent of his CAD (S1, S3).

Stents were placed for diffuse atherosclerotic changes (S1) and inoperable triple-vessel coronary artery disease (CAD) which was identified via percutaneous transluminal coronary angioplasty. The RMCA was small, non-dominant, with subtotal occlusion. There was 10% luminal compromise of the LMCA. Heavy calcification was noted within all of the diagonals of the LAD, while the LAD itself was diffusely diseased with areas of ectatic dilation and moderate stenosis, 60-70%. There was an aneurysmal dilation in the proximal LAD and a bare-metal stent was deployed distal to the dilation, in the mid-LAD. The left circumflex (LCX) was the dominant vessel and the AV segment was diffusely dilated and ectatic. The first and second obtuse marginal (OM1 and OM2) were 100% occluded and were noted to fill retrograde. A cutting balloon was unable to cross the area of disease in the both the OM1 and OM2. The OM3 had multiple stenotic regions with the worst being 90% occluded and a bare-metal stent was deployed at the location of the near-total occlusion. The posterior descending artery (PDA) was large and

 doi:10.20944/preprints202011.0668.v1

also diffusely atherosclerotic with multiple angiographic stenotic areas of varying severity; the worst located in the distal segments. During follow-up he reported little relief from the stent(s) and presented with angina for the first time.

An ECHO in March of 2010 showed a large wall-motion abnormality in the lateral and inferolateral walls. A low-normal left ventricular ejection fraction (LVEF), 40-50%, was also noted despite first line mediations, which were modified for maximal impact and failing. Medications at that time where: aspirin 325 mg, clopidogril 75 mg, atorvastatin 40 mg, niacin 500 mg, omega-3, and carvedilol 3.125 mg (S2). The atorvastatin was subsequently terminated and rosuvastatin 20 mg was initiated, as was lisinopril 25 mg. The carvedilol was also increased to 6.25 mg (1.5 tabs, daily). These changes in his pharmacologic treatment produced significant results in his functional capacity, as demonstrated by his LVEF of 60% during a cardiac cath later in April of 2010.

The patient underwent a cardiac re-catheterization in April 2010 to visualize his coronary anatomy, assess the patency of the previous stents, and to place drug-eluting stents in other areas of significant disease, if necessary. The left heart catherization demonstrated an RMCA with diffuse disease and total distal occlusion, LMCA with 40% occlusion, and an LCX with a fully occluded diagonal OM1 with a patent bare-metal stent in the proximal-OM3. The bare-metal stent in the mid-LAD was also patent. The LAD-1, however, was functionally occluded with poor run-off; it is noted that the vessel originally supplied a large area of myocardium. Drug-eluting stents were not placed, and the patient continued to report significant episodes of pain and discomfort consistent with stable angina.

 doi:10.20944/preprints202011.0668.v1

In September 2010, he had his first exercise tolerance test (ETT) to assess performance and to quantify his ischemia (S3). The EKG showed 2mm ST depressions, exercise-induced PVCs, and the test was abandoned.

In 2011, the patient underwent a SPECT study; Using a modified Bruce protocol, he completed 2 minutes of stage III until he began to experience significant pain. The patient chose to continue the test using regadenosine to ensure complete vasodilation. The EKG showed diffuse 1.5mm ST depression (S3). The ischemic changes first presented at the end of stage III of the modified Bruce protocol and were present up to 4 minutes in the recovery phase; they reversed to baseline after administration of aminophylline. Partial inferior wall scarring was noted; the LVEF was 54%. The SPECT ETT myocardial perfusion imaging study showed a mild intensity small-sized ischemic anterior wall defect extending from the mid to basal segments, a large size moderate intensity ischemic defect involving the anterolateral, inferolateral wall extending form the mid to the basal segments, and a small size mild to moderate intensity ischemic defect in the inferior wall. Compared to the prior test from 2010, the apical ischemia was no longer present, and the left ventricular wall hypokinesis was improved.

His medical records indicated persistent, recurring, chronic angina that would wax and wane in both severity and frequency, until progressing to unstable angina UA in 2012. As previously indicated, he has failed all first- and second-line pharmaceutical poly-pharmaceutical therapies. Most notably was the addition of ranolazine, which helped keep his chronic angina under moderate symptomatic control for several years. Ultimately, similar to other medications, ranolazine was modified for maximal impact and failed.

 doi:10.20944/preprints202011.0668.v1

In late October of 2017, the patient sought evaluation for medicinal cannabis (MC). On initial visit, he presented with chronic chest pain due to UA that has not been totally relieved with long term morphine treatment (morphine IR,15 mg/8hrs) and cardiac medications (rosuvastatin, amlodipine, clopidogril, ranolazine, aspirin, carvedilol, lisinopril, and zolpidem; S2). His chest pain was 3/10 during evaluation but reported it may reach a level of 7/10 and would radiate to the left side of his chest. The patient says he was unable to walk long distances or perform mild/moderate physical activity. His symptoms were usually relieved by rest. He would, however, also experience frequent occurrences of angina unprovoked by physical activity or exertion, thus defining the presence of UA. He was started on MC at that time.

In late November 2017, the patient was seen for his first follow-up and presented with a decrease in the frequency of his chronic pain (CP). He stressed how the pain used to occur a few times/day and is now noticeably less often. He was also able to walk more than he previously was, but he still cannot do any strenuous activity. He was using a combination of high THC and low CBD strains (1:340 CBD:THC). (S4). It was discussed that he should be decarboxylating his MC and using it in edible form. The patient was able to reduce his morphine dosage from every 8 hours to once per day (qd morphine IR,15 mg).

He returned in late December 2017 without any new significant relief compared to the previous months progress. He would still get a feeling of tightness across his chest and need to sit down (q2/mo). It was recommended that he try a high CBD strain (1.2:1 CBD:THC) in combination with the previous THC strain via edible butter extraction bi daily (S4).

 doi:10.20944/preprints202011.0668.v1

Early February 2018, the patient reported his pain was down from the old quality and character of sudden pain (even at rest), reported as a 6/10. Now described as a more consistent quality of dull pain rated at 3/10. He had been eating the recommended combo on toast 2-3x/day (t.i.d.) and reports being happier during the day. He was still using morphine once daily (qd morphine IR,15 mg). Overall, his chest discomfort and pressure were down 50%.

During his follow up in the beginning of March 2018, he recounted now going days without pain. The patients' CP was reduced from a few times a day to a few times a week but is dull and not sudden or debilitating like the past. It was discussed to stop the morphine if the MC is effectively controlling his CP. Later that week, the patient had a follow up with his cardiologist and they were both in agreement to continue using the MC if it his helping his UA and CAD symptoms, as well as reducing his dosage of morphine.

During his follow-up with cardiology, he was started on two new medications losartan and isorbide mononitrate; the latter of which is known to mitigate reflex tachycardia and would be beneficial in a patient utilizing cannabis for CHF. It is also noted that he presented with edema but does not have jugular vein distention. He was referred for follow-up testing, and in April of 2018, the patient underwent another ETT (S3).

The EKG showed no evidence of exercise induced arrhythmias (although a rare PVC was present) and there were no signs of ischemia changes, a significant improvement (i.e. any ST changes were less than 1 mm and did not fulfill criteria for ischemia). Together, these findings mark improved functional capacity.

 doi:10.20944/preprints202011.0668.v1

On his next Primary Care follow-up visit, in mid-May 2018, he had been off morphine for six days and controlling his symptoms using the recommended combo of high dose CBD oil daily (td) and THC butter 2-3 times daily (t.i.d.). He described the pain as no longer crippling and sees an increase in his daily functioning and overall activity, i.e. he was able to walk more and perform more strenuous activity.

Early July 2018, he was completely off morphine (morphine IR,15 mg/8hrs) since April using the recommended combo of high dose CBD oil and THC butter, as outlined above. His chest pain is significantly less frequent (2x/d from > 5x/day before treatment) and less intense (now a dull pain and numbness that travels to the left arm and back, about 4/10). He reports that his last bad day was 6-weeks prior (mid-May 2018) and rated the pain on that occasion as a 9/10.

As of late March 2019, the patient reported only two episodes of chest pain since July 2018. The last one occurred in early March 2019 and was associated with a significantly emotional event. The patient is still opioid free, for ten months, and utilizes a premixed combination of high-dose CBD hemp oil and a low dose of THC (15:1 CBD/THC) or the recommended extraction (1.2:1 CBD:THC), as outlined above. There have been no changes to his medications.

Discussion:

The observed cardiovascular benefits of MC outlined here in this case support current trends in the literature, i.e. cell culture [5], systematic reviews [6], receptor cloning and agonist/antagonist studies [7-9]. The case also supports the hypothesis that components of cannabis appear to be cardioprotective [4-9], operating via a vast distribution of the endocannabinoid system (ECS) and non-cannabinoid secondary messenger systems.

 doi:10.20944/preprints202011.0668.v1

Cannabis-induced acute MI (AMI), however, is a paradoxical feature of cannabis; occurring in a small percentage of users without a history of CAD or other appreciable factors [3, 10-12]. The leading hypothesis for AMI involves ST segment abnormalities and 'hyper stimulation of vagal tone' [3]. Nevertheless, the mechanism, epidemiology, and prevalence remain elusive.

Starkly contrasting cannabis-induced AMI, emerging data explores a multifactorial role of MC in the treatment of UA and CAD via modulation of the ECS, CB_1 and CB_2. Altered expression of the CB_1 and CB_2 receptors has been demonstrated in the myocardium of mice, as well as in human cell culture, for models of cardiovascular disease, congestive heart failure (CHF), and ischemic insult [3-5].

Administration of low-dose THC, however, protected the myocardium from ischemic damage [4]. These findings were supported by lower systemic troponin and a reduced ischemic infarct [3]. The myocardium of a healthy left ventricle is rich in CB_1 and CB_2 in nearly identical quantities. Meanwhile, cell culture studies have demonstrated that this ratio of CB_1:CB_2 is significantly altered following cardiovascular pathology.

In cells from patients with CHF, CB_1 was slightly, but significantly, downregulated while CB_2 was upregulated [5]. Cell culture studies from patients with MIs, and large ischemic insults, showed no change in CB_1 and an upregulation of CB_2 [4, 5]. In addition, CB_1 antagonism promotes cardiac remodeling following MI [5]. Thus, the downregulation of CB_1 observed in CHF might be maladaptive.

Recent studies have supported the role of CB_1 and CB_2, located systemically and in the cardiovascular system, as exhibiting both pathologic and protective effects depending on receptor agonism/antagonism [3] with a strong correlation for CB_1

 doi:10.20944/preprints202011.0668.v1

243 inhibition and therapeutic benefits in cardiovascular pathology [4]. The ECS has a
244 functional role in coagulation and atherosclerosis.

245 Platelet cell membranes, and atherosclerotic plaques, have both CB_1 and CB_2 [4].
246 Low-dose oral THC inhibits atherosclerosis progression via pleiotropic
247 immunomodulatory effects in apolipoprotein-E knockout models [9], as well as inhibiting
248 lymphoid proliferation and macrophage chemotaxis, in a dose dependent manner [4, 9].
249 This effect can also be inhibited by a CB_2 antagonist [4]. A similar function was observed
250 for CB_2 in vascular smooth muscle cells in coronary arteries. Depending on receptor
251 activation, the ECS can promote destruction of plaques; a potential druggable target.

252 THC is a CB_1 partial agonist, known to promote systemic vasodilation in addition
253 to negative inotropy[4]. CBD, however, has little affinity for CB_1 or CB_2. Instead, acting
254 as a CB_1 inverse agonist indirectly via GPCRs. CBD also acts on non-cannabinoid
255 targets, i.e. as a GPR-55 antagonist and 5-HT_{1A} agonist. CB_1 blockade is a proposed
256 druggable target in cardiomyopathies because inhibition reverses negative inotropy [4].
257 We hypothesize that the high CBD content in the patient's cannabis oil, in conjunction
258 with his standard cardiac care, to be responsible for his improved functional capacity.

259 Several hypotheses outline the importance of upregulated CB_2 in cardiomyocytes
260 following cardiovascular insult. Most notably, CB_1 and CB_2 are hypothesized to play a
261 dual role in regulating positive/negative inotrope through GPCRs. Specifically, the
262 inhibitory Gi and Go proteins, and/or Gq proteins that resemble myocardial 5-HT_{2A} [5].
263 CB_2 agonists are even known to be cardioprotective during times of acute ischemia,
264 limiting myocardial damage during prolonged oxygen deprivation. An increase in CB_2
265 might be responsible for the compensatory and beneficial mechanisms observed in CHF

 doi:10.20944/preprints202011.0668.v1

[5]. All of which can be of considerable benefit for a heart, such our patients', that never adequately re-vascularized.

Conclusion:

This case report supports MC as an adjunctive treatment for UA and CAD. We hypothesize that our patients' improved METs, UA, CP, reduced ischemic changes during stress tests, and overall increase in cardiovascular health/functional capacity, to be the result of a multifactorial mechanism. The mechanism of the ECS, its role in CV function, CP, and other systemic pathological states, have yet to be fully elucidated. However, it is possibly the result of mixed CB_1 and CB_2 agonists/antagonists acting systemically on cardiomyocytes, vascular smooth muscle, and inflammatory cytokines/pro-inflammatory cells. Thus, increased appreciation of the involvement of the ECS in cardiac function and CP could result in greater use of agents targeting this system for CAD and related conditions.

List of abbreviations:

Medicinal cannabis (MC), unstable angina (UA), coronary artery disease (CAD), transient receptor potential cation channel subfamily V member 1 (TRPV1), heart rate (HR), endocannabinoid system (ECS), anandamide (AEA), 2-Arachidonoylglycerol (2-AG), acute myocardial infarction (AMI), atrial fibrillation (AFib), percutaneous transluminal coronary angioplasty (PTCA), exercise tolerance test (ETT), left anterior descending artery (LAD), left main coronary artery (LMCA), right coronary artery (RMCA), left ventricular ejection fraction (LVEF), 2D echocardiogram (ECHO), obtuse marginal 3 (OM3), posterior descending artery (PDA), electrocardiogram (EKG),

 doi:10.20944/preprints202011.0668.v1

288 METs (Metabolic Exercise Test), chronic pain (CP), cannabidiol (CBD), Δ^9-

289 tetrahydrocannabinol (THC).

290 **Declarations:**

291 **Ethics approval and consent to participate:**

292 Geisinger Institutional Review Board (GIRB)

293 Geisinger Medical Center 100 N.

294 Academy Avenue Danville, PA 17822-3069

295 Tel: 570-271-8663

296 Study #2018-134 *"A Retrospective Analysis of Access to Medical Cannabis"*

297

298 The above proposal was reviewed on June 29, 2018. The proposal did not appear to

299 involve "human subjects" as defined in 45 CFR 46. 102(f); and therefore, is not subject to

300 oversight by the Institutional Review Board. This research activity determination of

301 "research that does not involve human subjects" required that the investigator and study

302 personnel only receive information that is totally de-identified, meaning the data did not

303 contain any direct or indirect HIPAA identifier.

304

305 **Consent for publication:**

306 Consent was obtained by the patient and a signed deceleration of consent is available

307 upon request.

308

309 **Availability of data and material:**

310 'Not applicable.'

311

312 **Competing interests:**

B.J.P. has received research support from the Center for Wellness Leadership, Fahs-Beck Fund for Research and Experimentation, Pfizer, and the National Institute of Drug Abuse and travel from the Wellness Connection of Maine, Hereditary Neuropathy Foundation, and Patients Out of Time organizations. He serves (pro bono) on the advisory board for the Center for Wellness Leadership. His wife ss employed by Garlic Acres, a greenhouse that produces CBD products. The remaining authors have no competing interests and nothing to disclose.

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Authors' contributions:

B.L.S. is the primary care physician for the patient. He initially collected all of the primary care data. He analyzed and provided the patients past medical files, relevant for the case. His staff de-identified all files and data. G.M.D and M.A.I. compiled ECG, ETT, and METs findings. G.M.D and M.A.I. designed the figures, prepared them for publication, and made substantial edits to the document. B.J.P. made significant contributions to editing the case report. B.V.E. collected, reviewed, and processed all patient files. B.V.E. wrote the case report, making/approving final edits, and maintained the collaborative network. All authors read and approved the final manuscript.

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Supplemental Tables:

Supplemental Table 1 – Summary of Cardiac History (2009-2010).

	Procedure	Findings
December, 2009	CT Angiogram	Calcification in the LMCA and the proximal LAD; estimated at least a 50% luminal compromise. Disease in the RMCA was also noted.
January, 2010	ECHO	Normal left ventricular systolic function.
January, 2010	Cardiac Catheterization	The RMCA was small, non-dominant, with subtotal occlusion. There was 10% luminal compromise of the LMCA. Heavy calcification was noted within all of the diagonals of the LAD, while the LAD itself was difflusely diseased with areas of ectatic dilation and moderate stenosis, 60-70%. There was an aneurysmal dilation in the proximal LAD and a bare-metal stent was deployed distal to the dilation, in the mid-LAD. The left circumflex (LCX) was the dominant vessel and the AV segment was diffusely dilated and ectatic. The first and second obtuse marginal (OM1 and OM2) were 100% occluded and were noted to fill retrograde. A cutting balloon was unable to cross the area of disease in the both the OM1 and OM2. The OM3 had multiple stenotic regions with the worst being 90% occluded and a bare-metal stent was deployed at the location of the near-total occlusion. The posterior descending artery (PDA) was large and also diffusely alherosclerotic with multiple angiographic stenotic areas of varying severity; the worst located in the distal segments.

LMCA, left main coronary artery, LAD, left anterior descending artery. RMCA, right main coronary artery.

 doi:10.20944/preprints202011.0668.v1

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Supplemental Table 2- Medications and dosages (2009-2019).

Date	Medication	Dosage	Interval	Comments
12/30/2009				Patient Presents for Second Opinion
	Atorvastatin	40 mg	Daily	-
	Metoprolol	50 mg	2x, Daily	-
	Aspirin	325 mg	Daily	-
1/8/2010				Echo/Cardiac Cath/Stents Placed
	Aspirin	325 mg	Daily	Dual Anti-lately therapy for 1 mo. Following stent placement. Must maintain Clopidogrel therapy for at least 9 mo.
	Clopidogrel	75 mg	Daily	Dual Anti-platelet therapy for 1 mo. Following stent placement. Must maintain Clopidogrel therapy for at least 9 mo.
2/17/2010				Nuclear Stress Test- Follow Up
	Atorvastatin	40 mg	Daily	Medication modified for maximal impact. Switched from Atorvastatin, which he failed, to Rosuvastatin.
	Metoprolol	50 mg	2x, Daily	
	Aspirin	325 mg	Daily	Now recommend for life-long treatment
	Clopidogrel	75 mg	Daily	Now recommend for life-long treatment
	Rosuvastatin	20 mg	Daily	Initiated
	Niacin	500 mg	2x, Daily	Initiated
	Omega-3	1000 mg	2x, Daily	Initiated
2/24/2010				
	Carvedilol	3.125 mg	Unknown	Initiated
	Metoprolol	50 mg	2x, daily	Terminated
3/17/2010				ECHO/Doppler- Follow Up
	Aspirin	325 mg	Daily	Life-long treatment

 doi:10.20944/preprints202011.0668.v1

	Clopidogrel	75 mg	Daily	Life-long treatment
	Rosuvastatin	20 mg	Daily	-
	Niacin	500 mg	2x, Daily	-
	Omega-3	1000 mg	4x, Daily	Increased from twice, to four times.
	Carvedilol	6.25 mg	1.5 Tabs, Daily	Carvedilol dosage increased
	Lisinopril	25 mg	Daily	Initiated
5/26/2010				
	Aspirin	325 mg	Daily	Life-long treatment
	Clopidogrel	75 mg	Daily	Life-long treatment
	Rosuvastatin	20 mg	Daily	-
	Niacin	500 mg	2x, Daily	Terminated due to adverse side effects
	Omega-3	1000 mg	4x, Daily	-
	Carvedilol	6.25 mg	1.5 Tabs, Daily	-
	Lisinopril	25 mg	Daily	-
9/15/2010				ETT
	Aspirin	325 mg	Daily	Life-long treatment
	Clopidogrel	75 mg	Daily	Life-long treatment
	Rosuvastatin	20 mg	Daily	-
	Omega-3	1000 mg	4x, Daily	-
	Carvedilol	12.5 mg	2x, Daily	Carvedilol dosage increased
	Lisinopril	25 mg	Daily	-
10/5/2010				ECHO/Doppler- Follow Up
	Aspirin	325 mg	Daily	Life-long treatment
	Clopidogrel	75 mg	Daily	Life-long treatment
	Rosuvastatin	20 mg	Daily	-
	Omega-3	1000 mg	4x, Daily	-
	Carvedilol	12.5 mg	2x, Daily	-
	Lisinopril	25 mg	Daily	-
1/17/2011				
	Aspirin	325 mg	Daily	Life-long treatment

 doi:10.20944/preprints202011.0668.v1

	Clopidogrel	75 mg	Daily	Life-long treatment
	Rosuvastatin	40 mg	Daily	Rosuvastatin dosage increased
	Omega-3	1000 mg	4x, Daily	-
	Carvedilol	12.5 mg	2x, Daily	-
	Lisinopril	25 mg	Daily	-
3/16/2011				
	Aspirin	325 mg	Daily	Life-long treatment
	Clopidogrel	75 mg	Daily	Life-long treatment
	Rosuvastatin	40 mg	Daily	Rosuvastatin dosage decreased due to muscle aches and pains.
	Omega-3	1000 mg	4x, Daily	-
	Carvedilol	12.5 mg	2x, Daily	-
	Lisinopril	25 mg	Daily	-
5/6/2011				Nuclear Stress Test- Follow Up
	Aspirin	325 mg	Daily	Life-long treatment
	Clopidogrel	75 mg	Daily	Life-long treatment
	Rosuvastatin	20 mg	Daily	-
	Omega-3	1000 mg	4x, Daily	-
	Carvedilol	12.5 mg	2x, Daily	Carvedilol dosage increased. Additional 6.25 mg, taken at night. Continued 12.5 mg 2x, daily
	Carvedilol	6.25 mg	At night	Initiated
	Lisinopril	5 mg	Daily	Dosage decreased
7/18/2011				ECHO/Doppler- Follow Up
	Aspirin	81 mg	2x, Daily	Dosage decreased, Life-long treatment
	Clopidogrel	75 mg	Daily	Life-long treatment
	Rosuvastatin	20 mg	Daily	-
	Omega-3	1000 mg	4x, Daily	-
	Carvedilol	12.5 mg	2x, Daily	-
	Carvedilol	6.25 mg	At night	Terminated
	Lisinopril	5 mg	Daily	-
	Ranolazine	500 mg	Unknown	Initiated

 doi:10.20944/preprints202011.0668.v1

9/12/2011				
	Aspirin	81 mg	2x, Daily	Life-long treatment
	Clopidogrel	75 mg	Daily	Life-long treatment
	Rosuvastatin	20 mg	Daily	-
	Omega-3	1000 mg	4x, Daily	-
	Carvedilol	12.5 mg	2x, Daily	-
	Lisinopril	5 mg	Daily	-
	Ranolazine	500 mg	Unknown	-
1/10/2012				
	Aspirin	81 mg	2x, Daily	Life-long treatment
	Clopidogrel	75 mg	Daily	Life-long treatment
	Rosuvastatin	20 mg	Daily	-
	Omega-3	1000 mg	4x, Daily	-
	Carvedilol	12.5 mg	2x, Daily	-
	Lisinopril	5 mg	Daily	-
	Ranolazine	500 mg	2x, Daily	-
5/4/2012				
	Aspirin	81 mg	2x, Daily	Life-long treatment
	Clopidogrel	75 mg	Daily	Life-long treatment
	Rosuvastatin	20 mg	Daily	-
	Omega-3	1000 mg	4x, Daily	-
	Carvedilol	12.5 mg	2x, Daily	-
	Lisinopril	5 mg	Daily	-
	Ranolazine	500 mg	2x, Daily	-
10/27/2017				Initial Consultation for MC
	Rosuvastatin	20 mg	Daily	-
	Amlodipine	5 mg	Daily	Medication not seen in prior physician encounters, not a new prescription.
	Clopidogrel	75 mg	Daily	Life-long treatment
	Ranolazine	500 mg	2x, Daily	-
	Aspirin	81 mg	2x, Daily	Life-long treatment

 doi:10.20944/preprints202011.0668.v1

	Carvedilol	12.5 mg	Daily	-
	Lisinopril	10 mg	Daily	Dosage increased compared to previous records.
	Morphine	15 mg	2x, Daily	Medication not seen in prior physician encounters, not a new prescription either.
	Zolpidem	5 mg	Daily	-
11/22/2017				First Follow-Up- MC
	Rosuvastatin	20 mg	Daily	-
	Amlodipine	5 mg	Daily	-
	Clopidogrel	75 mg	Daily	Life-long treatment
	Ranolazine	500 mg	2x, Daily	-
	Aspirin	81 mg	2x, Daily	Life-long treatment
	Carvedilol	12.5 mg	2x, Daily	-
	Lisinopril	10 mg	Daily	-
	Morphine	15 mg	Daily	-
	Zolpidem	5 mg	Daily	Terminated
12/27/2017				Second Follow-Up- MC
	Rosuvastatin	20 mg	Daily	-
	Amlodipine	5 mg	Daily	-
	Clopidogrel	75 mg	Daily	Life-long treatment
	Ranolazine	500 mg	2x, Daily	-
	Aspirin	81 mg	2x, Daily	Life-long treatment
	Carvedilol	12.5 mg	2x, Daily	-
	Lisinopril	10 mg	Daily	-
	Morphine	15 mg	Daily	-
2/6/2018				Third Follow-Up- MC
	Rosuvastatin	20 mg	Daily	-
	Amlodipine	5 mg	Daily	-
	Clopidogrel	75 mg	Daily	-
	Ranolazine	500 mg	2x, Daily	-
	Aspirin	81 mg	2x, Daily	-
	Carvedilol	12.5 mg	2x, Daily	-

 doi:10.20944/preprints202011.0668.v1

	Lisinopril	10 mg	Daily	Terminated
	Morphine	15 mg	1x, Daily	-
3/6/2018				Fourth Follow-Up- MC
	Rosuvastatin	20 mg	Daily	-
	Amlodipine	5 mg	Daily	-
	Clopidogrel	75 mg	Daily	Life-long treatment
	Ranolazine	500 mg	2x, Daily	-
	Aspirin	81 mg	2x, Daily	Life-long treatment
	Carvedilol	12.5 mg	2x, Daily	-
	Morphine	15 mg	1x, Daily	-
3/16/2018				First Follow-Up with Cardiology- Post-MC
	Rosuvastatin	20 mg	Daily	-
	Amlodipine	5 mg	Daily	-
	Clopidogrel	75 mg	Daily	Life-long treatment
	Ranolazine	500 mg	2x, Daily	-
	Aspirin	81 mg	2x, Daily	Life-long treatment
	Carvedilol	12.5 mg	2x, Daily	-
	Morphine	15 mg	1x, Daily	-
	Losartan	100 mg	Daily	Initiated
	Isosorbide Mononitrate	30 mg	Daily	Initiated
	Montelukast	10 mg	Daily	-
5/17/2018				Fifth Follow-Up with MC
	Rosuvastatin	20 mg	Daily	-
	Amlodipine	5 mg	Daily	-
	Clopidogrel	75 mg	Daily	Life-long treatment
	Ranolazine	500 mg	2x, Daily	-
	Aspirin	81 mg	2x, Daily	Life-long treatment
	Carvedilol	12.5 mg	2x, Daily	-
	Morphine	15 mg	1x, Daily	Terminated
	Losartan	100 mg	Daily	-
	Isosorbide Mononitrate	30 mg	Daily	-

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	Montelukast	10 mg	Daily	-
	Clonazepam	0.5 mg	As needed	Initiated for morphine withdrawal symptoms
7/17/2018				Sixth Follow-Up with MC
	Rosuvastatin	20 mg	Daily	-
	Amlodipine	5 mg	Daily	-
	Clopidogrel	75 mg	Daily	Life-long treatment
	Ranolazine	500 mg	2x, Daily	-
	Aspirin	81 mg	2x, Daily	Life-long treatment
	Carvedilol	12.5 mg	2x, Daily	-
	Losartan	100 mg	Daily	-
	Isosorbide Mononitrate	30 mg	Daily	-
	Montelukast	10 mg	Daily	-
	Clonazepam	0.5 mg	As needed	
3/26/2019				Seventh follow-up with MC
	Rosuvastatin	20 mg	Daily	-
	Amlodipine	5 mg	Daily	-
	Clopidogrel	75 mg	Daily	Life-long treatment
	Ranolazine	500 mg	2x, Daily	-
	Aspirin	81 mg	2x, Daily	Life-long treatment
	Carvedilol	12.5 mg	2x, Daily	-
	Losartan	100 mg	Daily	-
	Isosorbide Mononitrate	30 mg	Daily	-
	Montelukast	10 mg	Daily	-
	Clonazepam	0.5 mg	As needed	-

 doi:10.20944/preprints202011.0668.v1

379

Supplemental Table 3 - Single-photon emission computerized tomography and Exercise Tolerance Test findings (2010-2018).

	Speed (miles/hour)	Grade (%)	Achieved Maximum Predicted Heart Rate (MPHR)	Total Exercise Time (min)	Stage	METs (Metabolic exercise Test)	Procedures	Notable EKG Findings
Feb-10	2.5 mph	12	96	5	-	7	SPECT	1.5mm ST depressions-horizontal to down sloping in the inferolateral leads.
Sep-10	1.7 mph	10	72	1 min 49 sec	1	4.6	ETT	2 mm ST depression, exercise induced PVCs, and the test was abandoned. He did not complete stage I.
Apr-11	-	-	-	2	3	-	SPECT	Began to experience significant pain and had not achieved the target heart rate. The test was converted to a pharmacologic stress test and Regadenosine was administered t ensure complete vasodilation.
Apr-11	1.7 mph	10	78	10	3	4.6	SPECT	0.5 mm ST depression in leads II, III, aVF,V3,V4, V5, and V6. The ischemic changes presented at the end of stage land were present up to 4 mins into the recovery phase, they reversed to baseline after administration of aminophylline.
Apr-18	1.8 mph	15	70	4 min 41 sec	2	6.1	ETT	No evidence of exercise induced arrhythmias (although a rare PVC was present) and there were no signs of ischemia.

SPECT, Single-photon emission computerized tomography; ETT. Exercise Tolerance Test; PVC, Pre-ventricular contraction

Supplemental Table 4- Medical Cannabis.

Strain	THC Concentration (%)	CBD Concentration (%)
Blueberry #32	14	0.04
Cannatonic	6	7
AK-47	18	0.05
Kush VIII	24	0.11
Orange Bud	17	0.05
S.A.G.E #20	23	0.07

THC, Tetrahydrocannabinol; CBD, Cannabidiol .

380
381

 doi:10.20944/preprints202011.0668.v1

Figure Legends:

Supplemental Table 1 – Summary of Cardiac History (2009-2010). Dsipalying the patients past cardiac medical history; specifically CT angiogram, ECHO, and cardiac catheterization findings.

Supplemental Table 2- Medications and dosages (2009-2019). Due to the complex nature of the patient's cardiac history (i.e. acute myocardial infarction, unstable angina, and congestive heart failure), he has an extensive history of poly-pharmaceutical treatment. Notably, he has a history of responding well to new medications when they are first introduced, producing significant results in his functional capacity. However, every first line mediation has been modified for maximal impact and failing.

Supplemental Table 3 - Single-photon emission computerized tomography and Exercise Tolerance Test findings (2010-2018). The patient has an extensive history of SPECT myocardial perfusion studies demonstrating ischemia of moderate severity involving a large area of the anterolateral, as well as the inferolateral and inferior segments of myocardium. Comparison of the patients two exercise tolerance tests, which utilized a modified Bruce protocol, demonstrates mark improved functional capacity. Compared to 2011, his test in 2018 showed no evidence of exercise induced arrhythmias and there were no signs of ischemia.

Supplemental Table 4- Medical Cannabis. The patient initially tried a variety of medical cannabis strains, including numerous combinations. He did not experience much symptomatic relief with strains that contained a high dose of THC. Once the patient began to utilize the high CBD strains, however, he began to demonstrate the most benefit. All THC and CBD percentages reported were provided to the physician by the state licensed dispensary where the patient purchases his products.