Cardiovascular Complications of Cannabis and Cannabinoid Use

Professor Paul I Dargan
Guy’s and St Thomas’ NHS Foundation Trust
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London, UK
Conflicts of Interest

- Member of the UK Advisory Council on the Misuse of Drugs
- Member of the EMCDDA Scientific Committee
- Advisor to the World Health Organisation on Cannabis
Presentations to the Emergency Department Following Cannabis use—a Multi-Centre Case Series from Ten European Countries

Alison M. Dines · David M. Wood · Miguel Galicia · Christopher M. Yates · Fridtjof Heyerdahl · Knut Erik Hovda · Isabelle Giraudon · Roumen Sedefov · Euro-DEN Research Group · Paul I. Dargan

- Case series acute cannabis toxicity (n=356)
- Generally mild-moderate neuropsychiatric toxicity

**BUT**

One pre-hospital asystolic cardiac arrest and fatality related to lone cannabis use in an 18y male
Cannabis and Cardiovascular Toxicity

Data on cardiovascular effects of cannabis from:

- [Animal studies – not considered in this talk]

- **Volunteer studies**: 1970s – 160+ published studies
  - \(\uparrow\text{HR} \) most reliable biomarker of cannabis exposure

- **In vitro studies**: 2000s to date
  - Interest in endocannabinoids and CVS risk

- **Case reports/series**
  - ACS/MI, arrhythmias, cardiovascular fatalities

- **Cohort studies**
  - ACS/MI, palpitations
SCRAs and Cardiovascular Toxicity

Data on cardiovascular effects of SCRAs from:

- [Animal studies – not considered in this talk]
- Volunteer studies: 1970s – 160+ published studies
  - ↑HR most reliable biomarker of cannabis exposure
- *In vitro* studies: 2000s to date
  - Interest in endocannabinoids and CVS risk
- *Case reports/series*
  - ACS/MI, arrhythmias, cardiovascular fatalities
- Cohort studies
  - ACS/MI, palpitations
Cannabis CVS – Volunteer Studies

- Dozens of studies - too many to cover in this talk!
- 9 volunteers: 10mg THC cigarettes vs cigarettes
  - 39% ↑HR for up to 60 minutes, p<0.001
  - Non-significant ↑ then ↓BP, with ↑peripheral blood flow (later studies confirm ↓PVR)
  - Propranolol prevented these effects
    - effects β-mediated; not consistent finding in all studies, ↓parasympathetic tone probably also important
Cannabis CVS – Volunteer Studies

- Cannabis related tachycardia related to CB-1 activity
  - Rimonabant (CB1 antagonist): 40mg/90mg doses attenuates cannabis related tachycardia (20mg THC cigarette)

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**Single and multiple doses of rimonabant antagonize acute effects of smoked cannabis in male cannabis users**

*Marilyn A. Huestis, Susan J. Boyd, Stephen J. Heishman, and Kenzie L. Preston*
Clinical Pharmacology and Therapeutics Research Branch, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD 21224, USA

*Denis Bonnet and Gerard Le Fur*
Sanofi-Aventis Inc., Montpellier 34184, France

*David A. Gorelick*
Clinical Pharmacology and Therapeutics Research Branch, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD 21224, USA
Tolerance to cannabis tachycardia develops over time

- Cannabis (16-30mg THC) vs placebo cigarettes daily
  - ↑HR 25-40% associated with cannabis initially
  - Decreasing magnitude & limited effect after 3-4 weeks daily cannabis at all doses

- Tolerance is lost within days of stopping cannabis

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*Tolerance to Marijuana-Induced Tachycardia in Man*

By

Robert J. Gibbins, Janet McDougall, C. G. Miles and Joan A. Marshman


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*Clinical Relevance of Cannabis Tolerance and Dependence*

Volunteer EP Study

- 6 volunteers: control vs IV THC 25mcg/kg
  (~5mg THC cigarette)
- ↓ sinus node recovery
  - Mean 943 ± 84ms to 617 ± 40ms, p<0.005
- ↑ S-A and A-V conduction
  - SA: mean 77 ± 8.9ms to 56 ± 9.7ms, p<0.005
  - AV: mean 81 ± 5.4ms to 71 ± 4.9ms, p <0.02

The electrophysiological effects of delta-9-tetrahydrocannabinol (cannabis) on cardiac conduction in man

American Heart Journal
December, 1977, Vol. 94, No. 6, pp. 740-747

Ronald H. Miller, M.D.*
Volunteer Study: Cannabis and MDMA

- 4-way double blind placebo controlled study in 16 volunteers (regular cannabis / MDMA users)
  - THC 4-6mg inhalation, MDMA 100mg capsules
- BP: THC no effect on $B_{sys}$ or $B_{diast}$ effects of MDMA
- $\uparrow$HR: THC 14/min, MDMA 20/min, THC/MDMA 30/min
**In Vitro** studies investigating cannabinoid related cardiovascular effects

- Increasing interest in the last 10-15 years in role of (endo)cannabinoids in cardiovascular dysfunction

<table>
<thead>
<tr>
<th>Component</th>
<th>Parameter</th>
<th>Function</th>
<th>Tissue</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>AEA</td>
<td>Compound</td>
<td>n.d.</td>
<td>V. saphena vascular endothelium</td>
<td>Billinger <em>et al.</em> (1998)</td>
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<tr>
<td>CB₁ receptor</td>
<td>mRNA, protein</td>
<td>n.d.</td>
<td>Left ventricular myocardium</td>
<td>Weis <em>et al.</em> (2010)</td>
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<td>Function</td>
<td>Inhibit of NAdr release</td>
<td>Atrial appendages</td>
<td>Molderings <em>et al.</em> (1999)</td>
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<tr>
<td></td>
<td>Protein</td>
<td>Decrease in contractility</td>
<td>Atrium</td>
<td>Bonz <em>et al.</em> (2003)</td>
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<td>Function</td>
<td>AEA- and 2-AG-stimulated NO release</td>
<td>Right atrium</td>
<td>Billinger <em>et al.</em> (1998); Stefano <em>et al.</em> (2000)</td>
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<td></td>
<td>Protein</td>
<td>AEA-stimulated NO release</td>
<td>Internal thoracic artery</td>
<td>Billinger <em>et al.</em> (1998)</td>
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<tr>
<td>CB₃ receptor</td>
<td>Function</td>
<td>Relaxation</td>
<td>Pulmonary artery</td>
<td>Kozlowska <em>et al.</em> (2007, 2008)</td>
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</table>

CB1 receptors plentiful in human coronary artery endothelial cells

CB1 activation: concentration dependent coronary artery endothelial cell death

Effect abolished by CB1 antagonists and also p38 and JNK-MAPK inhibitors
THC:
- Dose dependent ↑ cardiomyocyte NOx production
- Prevented by CB2 antagonist (SR2) but not by CB1 antagonist (SR1)

Orange staining indicates iNOS concentrations

CB-2 activation may therefore have a protective role

* * *

Volunteer and *In Vitro* Studies: Summary

- Volunteer studies in healthy young males:
  - Cannabis: tachycardia, mild hypertension followed by hypotension
  - CB1 receptors, also $\beta$-activity / parasympathetic tone
  - ↓ sinus node recovery ↑ S-A and A-V conduction

- More recent *in vitro* studies
  - CB1/ CB2 widely expressed in cardiovascular system
  - CB1: additional role in mediating ischaemic injury
  - CB2: complex role – vascular (NOx), neuro-hormonal, ischaemia-reperfusion, chemotaxis
Clinical and Epidemiological Data
Cannabis & Acute Coronary Syndrome/MI

- Dozens of case reports/series describing an *association* between acute cannabis use and ACS/MI
  - Generally young (15-40y) with limited/no risk factors for ischaemic heart disease
  - Many reports with normal coronary arteries on angiography
  - Toxicology screening confirming lone cannabis use

Effect of Cannabis on exercise time in patients with angina

- Double blind: *cannabis* (19.8mg THC/cigarette) vs *cigarette placebo*
- 10 volunteers 47.3 ± 6.1yr with angina and angiographically proven CAD (>75% one vessel)
- Bicycle exercise test: time to angina, HR, BP, COHb at baseline and after cigarette / cannabis cigarette
Table 1. Resting Mean Heart Rate, Systolic and Diastolic Blood Pressure, Product of Systolic Blood Pressure Times Heart Rate, and Venous Carboxyhemoglobin in the Control Periods and before and after Smoking of Marihuana (THC) and Placebo Marihuana (± 1 S.E.M.).

<table>
<thead>
<tr>
<th>PERIOD</th>
<th>HEART RATE</th>
<th>BLOOD PRESSURE</th>
<th>SYSTOLIC PRESSURE × HEART RATE</th>
<th>VENOUS CARBOXYHEMOGLOBIN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>per min</td>
<td>mm Hg</td>
<td>%</td>
<td>vol %</td>
</tr>
<tr>
<td>Control (1)</td>
<td>71.7 ± 1.1</td>
<td>119.5 ± 1.1</td>
<td>81.1 ± 0.9</td>
<td>8,578 ± 181</td>
</tr>
<tr>
<td>Before THC</td>
<td>70.5 ± 1.1</td>
<td>119.3 ± 1.0</td>
<td>81.0 ± 1.0</td>
<td>8,409 ± 158</td>
</tr>
<tr>
<td>After THC</td>
<td>100.6* ± 1.6</td>
<td>129.1* ± 0.8</td>
<td>86.5* ± 1.1</td>
<td>12,978* ± 227</td>
</tr>
<tr>
<td>Control (2)</td>
<td>73.1 ± 1.3</td>
<td>118.9 ± 1.2</td>
<td>81.0 ± 1.2</td>
<td>8,689 ± 163</td>
</tr>
<tr>
<td>Before placebo</td>
<td>73.7 ± 1.2</td>
<td>119.3 ± 1.1</td>
<td>81.3 ± 1.0</td>
<td>8,792 ± 160</td>
</tr>
<tr>
<td>After placebo</td>
<td>74.4* ± 1.2</td>
<td>119.6* ± 1.2</td>
<td>81.4* ± 1.1</td>
<td>8,901* ± 181</td>
</tr>
</tbody>
</table>

*p < 0.001.

Effect of Marihuana and Placebo-Marihuana Smoking on Angina Pectoris

Wilbert S. Aronow, M.D., and John Cassidy, M.D.

The New England Journal of Medicine

July 11, 1974
Exercise time

- Cannabis: ↓ 48%
- Cigarette: ↓ 9%
Cannabis & Acute Coronary Syndrome/MI

Large post-MI study

- 3882 interviewed median 4 days post MI
  - 3.2% cannabis in year before MI
  - 1.0% cannabis in 24h before MI
- Analysis controlled for obesity, smoking, hypertension

Triggers Myocardial Infarction by Marijuana

Murray A. Mittleman, MD, DrPH; Rebecca A. Lewis; Malcolm Maclure, ScD; Jane B. Sherwood, RN; James E. Muller, MD

Circulation. 2001;103:2805-2809
Comparative triggers of MI

Systematic review and meta-regression of triggers

<table>
<thead>
<tr>
<th></th>
<th>Prevalence of exposure</th>
<th>OR (95% CI)</th>
<th>PAF (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air pollution, 10 µg/m³ reduction (n=11)†</td>
<td>100%</td>
<td>1.02 (1.01-1.02)</td>
<td>1.57% (0.89 to 2.15)</td>
</tr>
<tr>
<td>Air pollution, 30 µg/m³ reduction (n=11)†</td>
<td>100%</td>
<td>1.05 (1.03-1.07)</td>
<td>4.76% (2.63 to 6.28)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>3.2%</td>
<td>3.1 (1.4-6.9)</td>
<td>5.03% (2.91 to 7.06)</td>
</tr>
<tr>
<td>Anger (n=4)†</td>
<td>1.5%</td>
<td>3.11 (1.8-5.4)</td>
<td>3.07% (1.19 to 6.16)</td>
</tr>
<tr>
<td>Cocaine use</td>
<td>0.04%</td>
<td>23.7 (8.1-66.3)</td>
<td>0.90% (0.28 to 2.55)</td>
</tr>
<tr>
<td>Coffee</td>
<td>10.6%</td>
<td>1.5 (1.2-1.9)</td>
<td>5.03% (2.08 to 8.71)</td>
</tr>
<tr>
<td>Emotions positive</td>
<td>1.0%</td>
<td>3.5 (0.7-16.8)</td>
<td>2.44% (-0.30 to 13.64)</td>
</tr>
<tr>
<td>Emotions negative (n=3)†</td>
<td>1.2%</td>
<td>4.46 (1.85-10.77)</td>
<td>3.92% (0.99 to 10.34)</td>
</tr>
<tr>
<td>Heavy meal</td>
<td>0.5%</td>
<td>7.00 (0.8-66)</td>
<td>2.69% (-0.09 to 23.00)</td>
</tr>
<tr>
<td>Marijuana</td>
<td>0.2%</td>
<td>4.8 (2.9-9.5)</td>
<td>0.75% (0.38 to 1.67)</td>
</tr>
<tr>
<td>Physical exertion (n=6)†</td>
<td>2.4%</td>
<td>4.25 (3.17-5.68)</td>
<td>6.16% (4.20 to 8.64)</td>
</tr>
<tr>
<td>Respiratory infection (n=4)†</td>
<td>0.4%</td>
<td>2.73 (1.51-4.95)</td>
<td>0.57% (0.17 to 1.29)</td>
</tr>
<tr>
<td>Sexual activity (n=2)†</td>
<td>1.1%</td>
<td>3.11 (1.79-5.43)</td>
<td>2.21% (0.84 to 4.53)</td>
</tr>
<tr>
<td>Traffic exposure</td>
<td>4.1%</td>
<td>2.92 (2.22-3.83)</td>
<td>7.36% (4.81 to 10.49)</td>
</tr>
</tbody>
</table>

OR=odds ratio. PAF=population attributable fraction. *Prevalence was based on control time window. It was estimated from the control group (for case-control studies) or the control period (for case-crossover studies). When several studies existed for a same trigger, the average prevalence of the risk factor was calculated by weighting by the sample size of each study. For triggers studied in more than one study, the prevalence was based on the weighted average. †OR based on pooled OR and prevalence based on weighted means. Individual estimates are given in tables 1 and 3.

**Table 2: Prevalence of exposure within the population, pooled OR, and PAF for the studied triggers of myocardial infarction**

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Public health importance of triggers of myocardial infarction: a comparative risk assessment

Tim S Nawrot, Laura Perez, Nino Künzli, Elke Munters, Benoit Nemery

*Lancet* 2011; 377: 732–40
Cannabis and long-term mortality in survivors of MI

- 3886 pts with MI, followed up for median 18 years
  - 519 (13.4%) fatalities: 22 (20.2%) of the 109 reporting cannabis use in the year prior to MI

- Cannabis use in the year prior to MI: trend to ↑mortality
  - ↑29% (95% CI 0.81-2.05), p=0.28

- Only looked at cannabis use in year prior to MI, didn’t consider cannabis use post-MI or use of other drugs ...


Marijuana Use and Long-Term Mortality among Survivors of Acute Myocardial Infarction

Lauren Frost, MD, Elizabeth Mostofsky, MPH, ScD, Joshua I. Rosenbloom, MD, MPH, Kenneth J. Mukamal, MD, MPH, and Murray A. Mittleman, MD, DrPH
Cannabis-related Arrhythmias

- Numerous reports of arrhythmias associated with cannabis use
  - Ventricular arrhythmias, Brughada syndrome
  - Atrial fibrillation
  - Arrhythmogenic sudden death
- Toxicological confirmation of lone cannabis
- Generally young individuals with no risk factors, normal coronary arteries and no other causes for arrhythmia

What about SCRAs?
SCRAs and Cardiovascular Toxicity

- Much more limited data

- *In vitro* studies – a few included an SCRA
  - Generally greater CB1 activity; differential CB1:CB2 activity probably also important
  - Further work required to investigate potential non-cannabinoid receptor activity

- No volunteer studies

- Clinical case reports / small series of acute SCRA related CVS toxicity
Tachycardia / hypertension in “1/3 to 3/4” cases

Reports of chest pain, acute myocardial infarction, cardiac arrest, ischaemic and haemorrhagic stroke
Myocardial Ischemia Secondary to Synthetic Cannabinoid (K2) Use in Pediatric Patients
Bradley C. Clark, MD\textsuperscript{1,2}, Justin Georgekutty, MD\textsuperscript{1,2}, and Charles I. Berul, MD\textsuperscript{1,2}

Four analytically confirmed cases of use of third-generation synthetic cannabinoid receptor agonists incorporating an adamantyl group
William Rook, Loretta Ford & Allister Vale

Acute myocardial infarction, associated with the use of a synthetic adamantyl-cannabinoid: a case report

Case Report
A Unique Case of Cardiac Arrest following K2 Abuse
Saif Ibrahim, Farah Al-Saffar, and Thomas Wannenburg

Can your heart handle the spice: A case of acute myocardial infarction and left ventricular apical thrombus
Mahek Shah *, Jalaj Garg, Brijesh Patel, Justin Guthier, Ronald S. Freudenberger
Conclusions

- Evidence from volunteer, clinical, epidemiological studies of an association between cannabis use & cardiac toxicity
  - Arrhythmias and sudden death, ACS/MI
    (Also evidence of cerebrovascular risk)
- Clinically significant effects
  - severe acute events are *probably* uncommon
  - BUT limited information on the scale of the problem
- Deserves further study particularly with legalisation and medical cannabis
- Reports of similar effects with SCRAs, particularly ‘3rd generation’ SCRAs