



## Cocoa Overconsumption and Cardiac Rhythm: Potential Arrhythmogenic Trigger or Beneficial Pleasure?

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### Abstract

The interrelation between arrhythmias and lifestyle factors is acknowledged. On the one side, there is a recognized interaction between atrial fibrillation and obesity, hypertension, dyslipidemia and type 2 diabetes mellitus. Saturated fats, excessive added salt, tea, coffee and energy drinks are often deleterious in rhythm disorders. The role of others, such as cocoa-rich foods, is less evident: several authors displayed the beneficial effect of the polyphenols content on numerous cardiovascular risk factors, while little is known about the potential link between diet and incident arrhythmias. Arrhythmias' most frequent risk factors include aging, hypertension, congenital cardiopathy, heart failure, valvulopathy, thyroid diseases and diabetes. Nevertheless numerous arrhythmias are not related to any of these risk factors: in these cases, immunological, functional and even nutritional mechanisms might be involved in dysrhythmias' genesis. Aim of this narrative review is to analyze the potential adverse effect of cocoa excessive consumption on cardiac rhythm and its mechanisms and to provide state-of-the-art knowledge on this topic.



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### Introduction


There is significant interest in the influence of diet in cardiovascular health. The effect of diet and lifestyle on cardiovascular is actually a public health priority. The examination of both dietetic patterns and single nutrients, represents the perfect approach to investigate the effects of foods with the synergistic interaction of their nutritive constituents.<sup>1</sup> Bioactive dietary elements, such as polyphenols,<sup>2</sup> terrestrial and marine carotenoids<sup>3-7</sup> and PUFAs,<sup>8</sup> show

antioxidant activities and substantially decrease many markers of oxidative stress, thus contributing to prevent numerous chronic disorders (especially cardiovascular diseases) by inhibiting the phlogistic responses.<sup>9-11</sup> Bacterial metabolites are produced from food components, which in turn emphasizes the importance of nutrition. Some of these metabolites, such as trimethylamine N-oxide, can exacerbate cardiovascular pathologies, while short-chain fatty acids seem to be protective metabolites.<sup>12</sup>

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In this respect, cocoa has displayed cardioprotective, anti-inflammatory and neuroprotective effect.<sup>13</sup> It can improve platelet function, blood pressure and fluidity because it enhances nitric oxide bioavailability. Numerous cocoa polyphenols (in particular flavonols) exert antioxidant effects. Cocoa is a rich source of high-quality antioxidant polyphenols, mainly catechins (29%–38% of total polyphenols), anthocyanins (4% of total polyphenols) and proanthocyanidins (58%–65% of total polyphenols). Other polyphenols from cocoa are: flavones (apigenin, quercetin, luteolin, kaempferol and their glycosides), polyphenolic acids (caffeic acid, chlorogenic acid, ferulic acid, coumaric acid, and syringic acid), caffeoyl-conjugates, stilbens (trans-resveratrol and its glycosides).<sup>14</sup> Their profile in cocoa varies depending of several factors, such as: plant genotype, geographic area,

ripeness degree of beans, cocoa processing.<sup>14</sup> Polyphenols can determine vasodilatation, also modulating phlogistic markers and cardiovascular status. Among flavonols, flavonoids are gaining considerable attention: they can modulate hepatic cholesterol metabolism by decreasing cholesterol absorption, thus resulting in decreased plasma lipids and atherogenic lipoproteins; they can both reduce the activity of enzymes belonging to the renin-angiotensin-aldosterone circuit and augment nitric oxide (NO) release, thus improving blood pressure and endothelial status. The habitual consumption of dark (cocoa content >55%) and extra-dark chocolate (cocoa content >70%), which are extremely rich in flavonoids, could improve endothelial health and decrease blood pressure, with an important cardiovascular protective potential.

**Table 1: Variability of amount (mg/kg of sample) of phenolics, flavonoids and methylxanthines in cocoa and chocolate<sup>10,16,74</sup>**

	Phenolics	Flavonoids	Theobromine	Caffeine	Theophylline
Cacao (raw ground paste)	6500	203-1233	2057-33000	230-5600	200
Dark chocolate	579	28-102	802-7500	80-875	< limit of detection
Milk chocolate	160	13	125-1004	20-56	< limit of detection

On the other hand, cocoa abuse can lead to the alteration of cardiac rhythm, such as tachyarrhythmias, atrial or ventricular fibrillation and supraventricular or ventricular tachycardia because of its caffeine amount.<sup>13</sup> Beside caffeine, other constituents can augment the sympathetic drive: all methylxanthines influence plasmatic levels of stress hormones (especially cortisol) and catecholamines (both adrenaline and noradrenaline).<sup>15</sup> The sympathetic adrenomedullary and the adrenocorticoid reaction to stress are enhanced: ingested methylxanthines stimulate the sympathetic nervous system, thus augmenting body temperature, systolic pressure, and accelerating heart rate.<sup>16</sup> Further, excess cocoa consumption can also lead to augmented plasmatic renin levels, which influence extracellular volume and, consequently, blood pressure.<sup>17</sup> Recent clinical case reports highlight a possible link between dietary components and heart conduction, thus recognizing excess cocoa-rich foods as a potential substrate for arrhythmias. For these reasons, this review was targeted to clarify whether cocoa over consumption

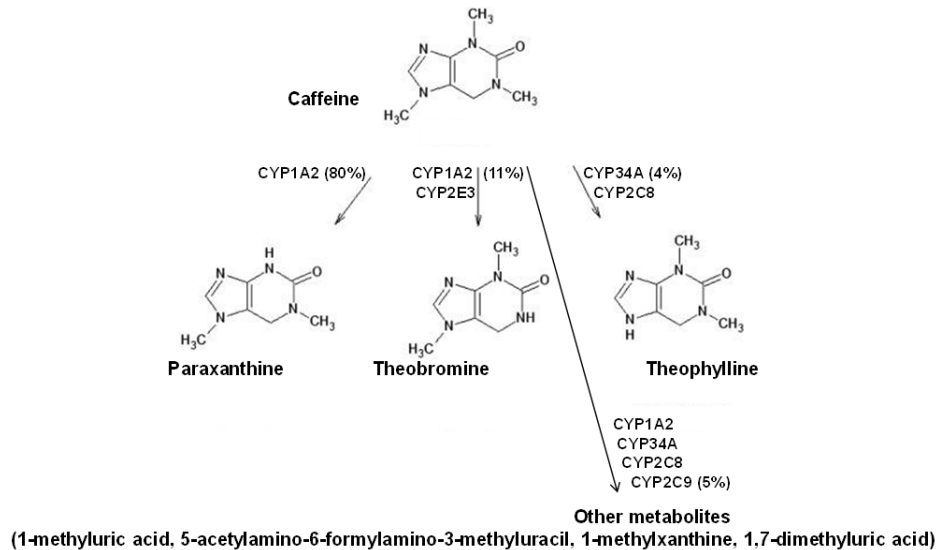
can influence cardiac rhythm potentially representing an arrhythmogenic trigger.

#### **Cocoa's Bioactive Constituents and Cardiovascular Side Effects**

Chocolate contains not only flavonols, useful substances for cardiovascular prevention, but also other bioactives with less studied cardiovascular side effects (table 1). In fact, cocoa originates from the roasted seeds of the plant *Theobroma cacao*, which contains a large amount of methylxanthine alkaloids.<sup>15</sup> Methylxanthines are phosphodiesterase (PDE) inhibitors, adenosine receptor antagonists and histone deacetylase inducers, with well-known anti-phlogistic activities. However, it is still debated whether these methylxanthines, in great amounts and in some particular conditions, might stimulate the conductive heart tissue. The competitive antagonism of the adenosine receptor after usual dietary methylxanthines intake is not generally linked to higher risk of arrhythmias. Nevertheless, in specific circumstances, sympathomimetic effects

of circulating catecholamines (responsible for the cardiac manifestations of caffeine overdose/toxicity) may determine tachyarrhythmias until ventricular fibrillation.<sup>18</sup> In this respect, case reports

of food-related atrial fibrillation, linked to high biogenic amines amount in ingested food and to excess chocolate ingestion, have been actually described.<sup>15,19</sup>



**Fig. 1: Metabolism of methylxanthines: paraxanthine represents the major human metabolite produced at more than 80% of a given oral dose of caffeine, followed by theobromine at approximately 11%, and theophylline at approximately 4%. Other metabolites have been reported as a result of further demethylation and oxidation; however, these account for less than 6% of total caffeine metabolites**

### Metabolism and Molecular Mechanism of Methylxanthines

Caffeine usually follows first-order linear kinetics, but non-linear kinetics can succeed in case of high doses and saturated metabolism. Paraxanthine is the main metabolite of caffeine biotransformation via the cytochrome CYP1A2, with potentially lower toxicity.<sup>20</sup> CYP1A2 is also responsible for the 1 and 7-demethylation of caffeine to the pharmacologically active molecules theobromine (which accounts for about 11%) and theophylline, which represents approximately 4% of caffeine metabolites (Figure 1). Other metabolites are 1-methyluric acid, 5-acetylamino-6-formylamino-3-methyluracil, 1-methylxanthine and 1,7-dimethyluric acid: more than 25 metabolites have been recognized in humans after caffeine ingestion, showing its complex metabolism.<sup>21</sup> Other CYP isozymes, such as CYP3A4, CYP3A5 and CYP2D6, are implicated in its metabolism at higher concentrations rather than those normally occurring after usual caffeine intake.<sup>20</sup>

There are significant human inter-individual differences in CYP1A2 activity, mostly due to genetics and partially to environmental factors. For example, smoking, coffee, ingestion of brassica vegetables, charcoal grilled meat, yerba mate, green tea, nuts, ginko biloba<sup>20, 22</sup> and some medications, such as omeprazole, can induce CYP1A2 activity; other medicaments, such as oral contraceptives, cimetidine, fluvoxamine, and apiaceae vegetables seem to inhibit it: these possible interferences could mask genetic background.<sup>23-25</sup> The analyses at the population level evidenced coefficient of variation values greater than 40% for CYP1A2 activities in humans, demonstrating high inter-individual variation.<sup>20, 21</sup> At physiologically relevant concentrations, the main proposed molecular targets of methylxanthines are the adenosine receptors (such as the subtypes A1, A2A, A2B, and A3).<sup>26</sup> These are G-protein coupled receptors, which activate G-proteins and lead to various effects upon signalling molecules, for example cAMP,

arachidonate, choline, inositol triphosphate and inositol triphosphate/diacylglycerol.<sup>20</sup>

Specifically, caffeine demonstrated to be a non-selective adenosine receptor antagonist with inhibition constant values of 8.5 and 7.8 mg/L for the adenosine A1 receptor subtype (mainly localized in brain, adrenal gland, heart and muscle) and A2A receptor subtype (mostly found in spleen, thymus, heart, lung and blood vessels).<sup>27</sup> The threshold for initial adenosine antagonism with caffeine is inferior than 1.94 mg/L.<sup>26</sup>

Methylxanthines have often been referred to as phosphodiesterase inhibitors, but they can interfere with this molecular target at concentrations widely exceeding normal chocolate and coffee consumption.<sup>20</sup> Consequently, phosphodiesterase inhibition may play some roles in caffeine effects in cases of large (potentially toxic) ingested amounts. Intracellular calcium release from cardiac muscle as a result of calcium-release channels activation has also been proposed as a possible mechanism for methylxanthines' effect: approximative concentrations from 971 to 3884 mg/L are necessary for substantial enhancement in calcium release, much higher than usual coffee or chocolate consumption.<sup>28, 29</sup> Thus, this might exert a pivotal role in methylxanthines' mechanisms maybe in case of large amount until toxic overdoses or in case of concomitant administration of certain medicaments. Similarly, caffeine also resulted to act as a potassium channel inhibitor at very elevated concentrations.<sup>30</sup> Other molecular targets, such as the  $\gamma$ -aminobutyric acid receptor type A, have been reported, but the inhibition constant value for caffeine is about 54.3 mg/L, that is also unlikely to be obtained after normal intake.<sup>26</sup> Apart from these mechanisms, methylxanthines have displayed to augment catecholamine levels, explaining several of its physiological effects: this action can be due to antagonism at the presynaptic A1 adenosine receptor and in the adrenal medulla as well.<sup>31, 32</sup> Methylxanthines have also been reported to exert cholinergic effects, since they inhibit acetylcholinesterase with a inhibition constant value of 34 mg/L: this concentration can hardly be reached, except in case of intoxication.<sup>33</sup> Thus, in cases of normal use methylxanthines can show simple mechanisms, in case of toxic doses, they can become much more complex molecules, eventually

interrelating with numerous molecular targets: this could clarify their potential side effects.

### **Caffeine**

Caffeine is a methylxanthine with several effects on vascular tissues. It is present in several medicaments, beverages (coffee, hot chocolate, cola drinks and tea) and cocoa-derived foods, which is metabolized and converted into three dimethylxanthines: theobromine, theophylline and paraxanthine by P4501A2.<sup>34, 35</sup> A combined consumption of cocoa, coffee, tea and cola drinks can bring to a notable mean daily dose of caffeine: superior than 2 mg/kg in an adult and about 0.7 mg/kg in a child.<sup>17</sup> At the moderate dose of 2 mg/kg of body weight or even less, caffeine stimulates alertness, concentration and psychomotor performance because it leads to higher intracellular calcium content in endothelium, due to increased expression of Nitric Oxide Synthase (eNOS) and increased NO production. Caffeine constitutes a central nervous system stimulant and a cardiovascular modulator and could improve sport performances in athletes, such as endurance ones.<sup>36</sup> It also stimulates Autonomic Nervous System: it inhibits the adenosine receptors, causing a reflex activation of the sympathetic system. In habitual coffee consumers, there is an activation of the sympathetic system, but the augmented sympathetic tone does not produce an important elevation in peripheral vascular resistance and in blood pressure: on the other side, these outcomes are reported in non-habitual consumers.<sup>37</sup>

The proposed background for these findings is the development of augmented tolerance to caffeine's effect in the acute setting. Caffeine binds to the A1 and A2 subtypes of the cardiac adenosine receptor; in intermittent doses, endogenously released adenosine could abbreviate atrial refractoriness, thus predisposing to arrhythmias. A kind of habituation could develop with long-term use, so that caffeine habitual intake may theoretically confer cardioprotection from heart rhythm alteration, by mitigating the activity of endogenous adenosine. A controlled animal trial reported that an escalating dose of caffeine increased propension for atrial fibrillation.<sup>38</sup> Another trial in the emergency department displayed that, among 68 subjects, who ingested caffeine had reduced responsiveness to a 6 mg bolus of adenosine in the treatment of supraventricular tachycardia.<sup>39</sup> Thus, at very high

doses (and in susceptible individuals even at low-moderate doses) caffeine could cause anxiety and adverse cardiovascular outcomes: an excessive catecholamine stimulation can determine extreme sympathomimetic effect, accountable for the cardiovascular effects of caffeine abuse, which in toxic amounts can cause tachyarrhythmias.<sup>40-42</sup> This potential arrhythmogenic risk after extreme consumption of cocoa-rich foods, coffee and cola drinks affects the supraventricular level.<sup>18</sup> Animal studies described atrial fibrillation and flutter after intravenous administration of 1-5 mg caffeine/kg of body weight.<sup>43</sup> Although cardiologists often suggest to routinely abstain from caffeinated foods/beverages in case of arrhythmias, this recommendation is not fully supported by evidence in human studies. Excessive doses of caffeine can exert sympathomimetic effects mediated by PDE's inhibition, which increases intracellular calcium, stimulating atrial automaticity, and enhancing depolarization-induced triggered activity. In addition, potential pro-arrhythmic actions of some energy drinks might also be induced by some "energy-boosting" additives, which were related to atrial and ventricular tachyarrhythmias and QT interval prolongation in various case reports.<sup>15, 44</sup>

Other observational studies suggest that regular moderate caffeine consumption (up to 300 mg, corresponding to 4 cups of coffee or 150 g dark chocolate) does not influence the risk of incident atrial fibrillation or ventricular arrhythmias, with some even suggesting a potential antiarrhythmic effect. This hypothetical advantage could be mediated by both inhibition of adenosine A1-A2A receptors (in fact adenosine shortens atrial refractoriness) and antioxidant activities, which target reactive oxidant species, which could stimulate adverse atrial remodelling.<sup>45</sup> Even if no clear interference of caffeine intake with interatrial and intra-atrial conduction intervals has been electrophysiologically displayed in humans, many subjects with paroxysmal atrial fibrillation point it as a trigger for arrhythmia.<sup>46</sup> However the cardiovascular response to chocolate's or coffee's caffeine depends on several aspects: the frequency of consumption, the total ingested amount, the velocity of consumption, the variable rate of gastrointestinal absorption and the individual effectiveness of liver metabolism.

These various factors are responsible for extremely variable responses in different subjects, with relevant inter-individual differences in plasmatic concentrations after administration of a standard dose of caffeine. This depends on variability in caffeine metabolism, mostly due to genetic polymorphisms, metabolic induction or inhibition of P-450 isoenzyme, eventual liver disorders, as well as weight, sex and other specific individual factors.<sup>47</sup> Multivariable models showed that young individuals, women, and subjects with a heart family history more commonly experienced various trigger-factors and that vagally-mediated triggers tended to cluster together.<sup>48</sup> In addition, other bioactive substrates from theobroma, specifically theobromine and theophylline, can exert a role in the wide variance in physiologic responses.

#### **Theobromine**

Theobromine and paraxanthine are cocoa-derived alkaloids, also present in tea and cola, which constitute the natural metabolites of caffeine in humans. Theobromine seems to be less adrenergically active than caffeine and a less powerful PDE inhibitor, with a lower affinity for adenosine receptors,<sup>49</sup> while it is a more potent cardiac stimulant with a longer estimated half-life (7-12 hours versus 2.5-5 hours of caffeine). Theobromine resulted to be a coronary artery dilator in humans at daily doses of 300 mg; a daily dose of 979 mg for 3 weeks demonstrated to reduce systolic blood pressure and to accelerate heart rate.<sup>50</sup> Theobromine displayed a slower diffusion across the blood-brain barrier compared to caffeine.<sup>15</sup> Its cardiostimulatory effect was described on fetal heart rhythm: 100 pregnant women with uncomplicated gestation underwent computerized fetal heart rate recording before and after intake of 30g dark chocolate with 80% cocoa. Cardiotocography parameters (fetal movements, uterine contractions, baseline fetal heart rate and its variability, frequency accelerations greater than 15 bpm for 15 seconds and number of decelerations) were assessed. Fetal heart reactivity resulted significantly higher after maternal consumption of dark chocolate with dose-depending effects.<sup>51, 52</sup> normal intake of theobromine in a standard portion of dark chocolate (about 40g), could promote cocoa benefits on mood, but higher quantities might be linked to adverse events.<sup>53</sup>

In addition, very recent studies identified theobromine, as a natural component able to brown white fat cells with promising anti-obesity effect: C57BL/6 mouse was fed with high fat diet and treated with theobromine: it attenuated diet-induced overweight by browning subcutaneous inguinal white adipose tissue and activating brown adipose tissue.<sup>54</sup> Theobromine actively interacted with the phosphodiesterase isoform PDE4D and reduced its activity in adipocytes, thus potentiating energy expenditure. This inhibition of PDE4D was mediated by  $\beta$ 3-adrenoreceptor signalling pathway, which is involved in lipolysis and consequently in the reduction of obesity and in the regulation of lipid metabolism.<sup>55</sup>

#### **Paraxanthine**

Paraxanthine is the main metabolite of caffeine, deriving from its demethylation and displaying a similar structure. This central nervous system stimulant is a psychoactive substance, responsible for the sympathomimetic effects of caffeine: it is a non-selective adenosine receptor antagonist, which increases epinephrine levels and, subsequently, diastolic blood pressure.<sup>56, 57</sup> Not only this adenosine antagonism, but also a cGMP-dependent PDE inhibition may be responsible for its stimulant effects.<sup>15</sup> In addition, paraxanthine displayed minor toxicity and lower anxiogenic activity, but it showed to contribute to caffeine's stimulating properties in a dose-dependent manner with a non-linear accumulation. After a repeated consumption of caffeine-rich foods/beverages, paraxanthine plasmatic levels even overcome caffeine levels in experimental animals,<sup>58</sup> even showing a pronounced inter-individual variability related to CYP1A2 enzymatic activity, responsible for its metabolism. It depends on both genetic (polymorphisms), and environmental factors, for example smoking, dietary habits and medicaments.<sup>59</sup>

#### **Phenylethylamine**

Phenylethylamine is a monoamine alkaloid (biosynthesized by enzymatic decarboxylation from the aminoacid L-phenylalanine) found in numerous foods, such as chocolate, mainly after microbial fermentation. After oral ingestion this organic compound experiences extensive first-pass metabolism by monoamine oxidase B: this avoids elevated concentrations from reaching the brain, even when significant doses are taken.<sup>60</sup>

Phenylethylamine is a neuromodulator in the central nervous system, with "amphetamine-like" pharmacological action. It releases norepinephrine and dopamine, with psychoactive and stimulant effect.<sup>61</sup> Cardiologists are actually recognizing the pharmacological and clinical relevance of phenylethylamine and "trace amines", biologically active amines (mainly based on phenylethylamine) occurring in human body in exiguous amount but present in medications and diet, especially in chocolate and wine.<sup>62</sup> Trace amines, represented by tyramine, tryptamine and beta-phenylethylamine, determine vascular constriction and increase systolic pressure: in fact they are frequently present in nasal decongestant medicaments. Their vasoconstrictor effect can be due to both an indirect mechanism (the release of noradrenaline from neuronal cells) and a direct vascular one: novel amine-associated receptors, the so-called TAARs, where trace amines can bind, have been identified in blood vessels.<sup>63</sup>

#### **Cocoa and Cardiac Rhythm: Methylxanthines as Arrhythmogenic Triggers in Dietetic Chocolate Abuse**

There are conflicting studies concerning the association between cocoa and cardiac rhythm. Ordinary chocolate intake is not normally linked to atrial fibrillation, but some sympathomimetic manifestations (due to circulating catecholamines) can be responsible for the cardiac effect of caffeine-overdose toxicity. In some particular conditions, this can produce tachyarrhythmias.<sup>13, 15, 18</sup> Methylxanthines are competitive antagonists of adenosine and might have arrhythmogenic potential in specific conditions, such as during beta-agonist therapy or in concomitance of amine-rich foods, because of their possible synergistic effect.

A case report of atrial fibrillation linked to chocolate abuse during salbutamol treatment showed an association between extreme chocolate ingestion and the sudden onset of an arrhythmia: a young woman displayed palpitations and an anamnestic history of asthma and chronic salbutamol inhalation in absence of cardiovascular disorders. The ECG evidenced an atrial fibrillation; the echocardiography showed a mild mitral regurgitation and an ejection fraction of 50%; a nutritional interview evidenced an excessive daily chocolate ingestion during the last 3 days. The following day, after the restoration of



sinusal rhythm, another ECG revealed a short PR tract, indicating an occult accessory pathway.

A normal cocoa ingestion is not usually related to the risk of arrhythmias, as well as a normal therapeutic dose of inhaled salbutamol, however a chronic salbutamol therapy shifts the cardiovascular autonomic regulation to a major sympathetic responsiveness and slight beta2-receptor tolerance; in addition, sympathomimetic manifestations due to circulating catecholamines can be responsible for the cardiac outcomes of caffeine- and theobromine-overdose toxicity. This means that methylxanthines present in the cocoa (after chocolate abuse), coupled with the concurrent short-acting beta agonist (during prolonged inhaled salbutamol treatment), were able to trigger this arrhythmia.<sup>19</sup>

Another recent case report evidences a possible link between dietary biogenic amines and recurrent atrial fibrillation onset in a 60-years old man in absence of a significant clinical history. The nutritional team instituted a low calories food protocol excluding any biogenic amines-rich foods; during the follow-up (24 months), a remarkable weight loss was reported (-14 kg) and no more arrhythmic episodes.

Similarly a case of paroxysmal supraventricular tachycardia precipitated by large amount of cocoa ingestion was described: an adult woman reported palpitations and shortness of breath after ingestion of a large amount of chocolate, in absence of remarkable medical history.<sup>64</sup> ECG evidenced a supraventricular tachycardia at 165 bpm; electrophysiology studies revealed atrioventricular nodal re-entry tachycardia, which was treated with radiofrequency ablation. In fact, methylxanthines, which are competitive antagonists of adenosine and might have arrhythmogenic potential in patient with underlying substrate. In humans, the cardiovascular sequelae of methylxanthines are attributable to the antagonism of adenosine A1 and A2 receptors, even at low concentrations resulting from the ingestion of a small dark chocolate amount (a bar, about 15 g) or coffee (a small cup, about 40 ml); higher concentrations are necessary for PDE inhibition or intracellular calcium mobilization.

Acute hemodynamic and neurohumoral modifications after an excessive methylxanthine intake (such as the augmented total peripheral resistance coupled

with slight acceleration in heart rate) may have an adverse cardiac output in patients undergoing some pharmacological therapies or with specific polymorphism and genetic profiles. The numerous clinical cases provide evidences for a potential link between foods and heart conduction, thus configuring the novel field of "nutri-arrhythmias" and arrhythmogenic foods, as the potential substrate or trigger of atrial fibrillation.

### **Paradoxical Effect of Cocoa**

Cocoa contains vascular regulatory compounds which are complexly intertwined to adjust endothelial functions. The role of cocoa's bioactives in endothelium is very complex: for example, caffeine can work as a NO stimulator or inhibitor, and as an inhibitor of NO second messenger cyclic guanosine monophosphate (cGMP) degradation. In severe arrhythmias due to methylxanthine intoxication, ventricular fibrillation has frequently been reported as the reason of death; frequent mechanisms for arrhythmias include augmented catecholamine levels and intracellular calcium, phosphodiesterase inhibition and antagonism of anti-arrhythmic adenosine receptors.<sup>65, 20</sup> Some paradoxical effects have also been reported: the paradox hypertension-hypotension and tachycardia-bradycardia, could be explicated by divergent molecular targets, which depend on the concentrations experienced and on variable physiological responses to various exposure levels. Specifically, hypertension can be determined by augmented catecholamines via presynaptic adenosine A1 receptor antagonism and by reduced vasodilatory effect of adenosine via adenosine A2 receptor antagonism, when methylxanthines' concentrations are in the therapeutic range.<sup>31, 32, 66</sup> On the contrary, hypotension could happen when much higher concentrations are reached, because of phosphodiesterase inhibition in cases of methylxanthines overdose and because of decreased cardiac output due to tachydysrhythmias.<sup>20</sup>

Similarly, a paradox bradycardia could derive from reflex bradycardia subsequent to augmented blood pressure. Tachycardia mostly occurred in case of methylxanthine intoxication, for example at doses of caffeine higher than 10mg/kg.<sup>20, 67</sup> This is possibly explained by beta 1-adrenergic agonism, linked to the augmented catecholamines, which results in higher cAMP levels via adenylyl cyclase activation. This process seems to be further triggered by

inhibition of phosphodiesterase, responsible for the reduced cAMP's degradation. In particular, caffeine's antagonism of adenosine A1 receptor could further strengthen the downstream effects of  $\beta$ 1-adrenergic agonism via augmented catecholamines level.<sup>31, 32, 68</sup>

On the other hand, numerous benefits have been reported on endothelium, mostly mediated by polyphenols.<sup>69-75</sup> Numerous experimental and epidemiological evidences highlight that cocoa polyphenols could decrease cardiovascular risks thanks to their antioxidant and anti-inflammatory properties, blood pressure lowering activity, antiplatelet, and anti-atherosclerotic effects, thus improving endothelial health.<sup>76</sup>

Additionally, very recent studies displayed that cocoa can prevent aortic stiffening and remodelling in diabetic animal models and reduce aortic oxidative stress: cocoa was shown to prevent sirtuin-1 (SIRT-1) depletion and increased NADPH oxidases (NOXs) and ROS generation.<sup>77, 78</sup>

Further clinical trials should examine the physiological effects of cocoa-rich foods excessive intake and their arrhythmogenic potential, considering that heart rate is a major determinant<sup>79-83</sup> of myocardial oxygen consumption; an increased heart rate (for example as a consequence of elevated sympathetic activity), decreases the diastolic coronary perfusion time and in some predisposed individual or in case of concomitant medicaments, may trigger arrhythmias events.

## Conclusion

An accurate evaluation of cardiac arrhythmias always makes necessary a research for underlying hidden causes: the entanglement of nutrition in cardiovascular diseases appears worthwhile to be studied in deep, considering methylxanthines and biogenic amines pro-arrhythmogenic potential.

For these reasons, clinical anamnesis in patients with new onset alteration of cardiac rhythm should also include an accurate food interview, in order to investigate any abuse of amines-rich foods, energy drinks and alcohol: their effects might be synergistic in influencing cardiac rhythm, defining the very novel and fascinating field of "nutri-arrhythmias".

## Author Contributions

Conceptualization, writing and editing M.A.G.; supervision and project administration, N.D. All authors have read and agreed to the content of the manuscript..

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## Conflict of interest

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