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Coffee Intake and Heart Failure

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Coffee Intake and Heart Failure

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Coffee Intake and Heart Failure

ORIENTADOR

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Ao meu Orientador,

pela constante disponibilidade e apoio durante a elaboração do trabalho.

Aos meus queridos Pais,

pelo exemplo de excelência académica, profissional e humana que sempre me proporcionaram.

ABSTRACT

Coffee is one of the most popular beverages of all time. Consumed worldwide in many different forms, the beverage consists of a mixture containing more than 1000 chemical compounds such as caffeine, chlorogenic acids, melanoidins and the diterpenes kahweol and cafestol. Heart failure prevalence is significant and is described as a global burden. Potential relationship between coffee consumption and risk of cardiovascular diseases, specific cardiovascular and all-cause mortality has been studied in the past, with conflicting results. Studies regarding safety of coffee consumption in patients with established heart failure are lacking. For the clinical and public health importance, we find relevant to question the impact of coffee consumption on such a vulnerable population. Through literature revision, the purpose of the present paper is to determine whether coffee intake in heart failure patients proves itself harmful or not. Potential adverse effects on blood pressure and peripheral vascular resistance seem to be counteracted by polyphenols and compounds with antioxidant capacity present in coffee. Additionally, coffee does not seem to trigger arrhythmia in heart failure patients with systolic dysfunction. Within low to moderate amounts, coffee does not seem to be harmful in heart failure, although it seems reasonable to discourage coffee in those who exhibit adverse effects after intake.

Key words: Coffee; Caffeine; Heart Failure; Cardiovascular Disease; Arrhythmia

RESUMO

O café é uma das bebidas mais populares de todos os tempos. Consumido em todo o mundo e nas mais diversas formas, o café consiste numa mistura de mais de 1000 compostos químicos, entre os quais a cafeína, os ácidos clorogénicos, as melanoidinas e os diterpenos caveol e cafestol. A prevalência de insuficiência cardíaca é elevada a nível mundial. A relação entre o consumo de café e o risco de doença cardiovascular, mortalidade cardiovascular e mortalidade global tem vindo a ser estudada, porém, com resultados controversos. Os estudos disponíveis quanto à segurança do consumo de café em pacientes com insuficiência cardíaca estabelecida são escassos. O objetivo do presente trabalho de revisão é determinar se a ingestão de café em pacientes com insuficiência cardíaca é ou não prejudicial. Potenciais efeitos adversos na pressão arterial e resistência vascular periférica parecem ser contrariados pela presença de polifenóis e compostos com propriedades antioxidantes no café. Além disso, o café parece não desencadear arritmias em doentes com insuficiência cardíaca por disfunção sistólica. Em quantidades ligeiras a moderadas, o café parece não ser prejudicial na insuficiência cardíaca , embora seja razoável desaconselhar a toma de café em indivíduos que apresentem efeitos adversos após ingestão da bebida.

Palavras Chave: Café; Cafeína; Insuficiência Cardíaca; Doença Cardiovascular; Arritmia

INTRODUCTION

Coffee is one of the most popular beverages of all time and is widely consumed worldwide in many different forms. It has been around for over 1000 years and consists of complex mixture containing more than 1000 chemical compounds.[1, 2] Coffee contains many biologically active substances such as caffeine, chlorogenic acids, melanoidins and the diterpenes kahweol and cafestol, capable of influencing consumer's health, for better or for worse.[3] The actual amount of chemicals absorbed into our organisms after every intake can vary tremendously according to coffee species, roasting time, brewing method as well as cup size and bioavailability of each compound's metabolites.[4]

Heart Failure (HF) is a clinical syndrome caused by structural or functional cardiac abnormalities, resulting in the inability to maintain adequate cardiac output.[5] Prevalence of HF depends on the definition applied and aetiologies vary considerably around the world. HF may be considered as the end stage of many heart disorders.[6] Nevertheless, the prevalence of the disease in developed countries is estimated around 1-2%[7] and the lifetime risk for developing HF at age 40 has been estimated to be 21% for men and 20% for women.[8]

Given that more than 400 billion cups of coffee are consumed annually[2] and the considerable prevalence of HF, we find it relevant, for both its clinical and public health importance, to question the impact of coffee consumption on the health of such a vulnerable population. In the last decade, many authors have attempted to establish potential relationship between coffee consumption and risk of cardiovascular diseases[1, 9-11] as well as specific cardiovascular and all-cause mortality [12, 13], but with conflicting results. To the best of our knowledge, not much work has been done on the safety of coffee consumption in patients with pre-established HF.

Can patients with HF safely drink coffee or should clinicians advise them not to? By focusing on the physiological effects of coffee components and the adaptive response mechanisms in HF, the aim of this review is to determine whether coffee intake in these patients proves itself harmful or not.

METHODS

For this review, an initial database search was conducted on MEDLINE using "Coffee" AND "Heart failure" as the search query on 02/09/2017. Research criteria applied included journal medline indexation, english language and literature based on human studies. Thirty-eight articles were generated in this search, 12 were excluded based on their abstract and 10 excluded after fully reading the remaining papers. From the initial search, 16 relevant papers were selected and reference lists were also scanned. Collateral research deemed relevant was selected by manual search, in order to further explore the biochemistry of coffee and pathophysiology of HF.

COFFEE AND ITS BIOLOGICALLY ACTIVE COMPONENTS

Coffee

Coffee consists of a vast mixture of biologically active substances such as caffeine, chlorogenic acids (CGAs), melanoidins and diterpenes. The two main types of green coffee beans used for the manufacture of coffee are *coffea arabica* and *coffea canephora* (also known as *robusta*), used for 70% and 25% of coffee production worldwide, respectively.[4] Both species have different compositions. Whereas *coffea arabica* bean contains more lipids, *coffea robusta* contains more polyphenols and caffeine (between 1.7 and 4.0% versus 0.8 and 1.4% in *coffea arabica*).[2]

Different preparation methods can alter the final composition of coffee. During the roasting process in particular, many compounds are formed and others suffer degradation.[3] Broadly, coffee preparation can be filtered or unfiltered. Depending on the method employed, several types of coffee can be obtained. Drip-filtered coffee and the common *espresso* are examples of filtered coffee, whereas boiled coffee (eg. Turkish or Arabic coffee) is unfiltered.[10]

Portugal is among the top 10 European coffee-drinking nations.[14] An average consumption of 11,8g of coffee per person per day was estimated among the Portuguese.[15] This is roughly equivalent to 2 standard *espressos* a day, a coffee preparation type that is popular in Portugal.

Boiled, unfiltered coffee has been found to contain greater amounts of total lipids than types of filtered coffee.[16] In fact, a systematic review and meta-analysis performed using 12 randomized controlled trials has shown that the intake of unfiltered coffee contributes to the increase in total cholesterol, low density lipoprotein cholesterol and triglyceride levels.[17]

As is predictable, variability in cup serving sizes is seen amongst different coffee preparation types. For instance, the capacity of a cup of drip-filtered coffee has been reported to be around 207ml, whereas a standard *espresso* usually contains around 45 to 60ml of coffee.[1]

Coffee's effects on the cardiovascular system are unquestionable and multiple attempts have been made to study its consequences (**Figure 1).** Acute elevations in blood pressure have been described after coffee intake, to a lesser extent compared with studies using caffeine alone, suggesting that other compounds in coffee might counteract caffeine's pressor effect. [18] On the other hand, a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies did not find association between coffee consumption and raised blood pressure levels (both diastolic and systolic) or increased risk of hypertension.[19] Coffee influence in the glucose metabolism and insulin sensitivity have also been a reported by numerous studies in past years. A systematic review and meta analysis of 9 cohort studies concluded the risk of developing Type 2 Diabetes Mellitus to be lowest in individuals with heavy coffee consumption (≥6 cups/day) compared to subjects with low coffee intake (<2 cups/day). [20]

Caffeine

Caffeine is coffee's most well known component. In fact, the use of coffee (the beverage) and caffeine (a chemical compound) as synonyms is a common misconception also present in biomedical literature. Caffeine (1,3,7 – trimethylxanthine) is a xanthine alkaloid naturally occurring in green coffee beans.[10] Amongst chemicals present in coffee, only caffeine is thermally stable enough to resist excessive roasting.[2] Caffeine content is highly variable among different coffee species, preparation methods and cup size.

A cup of coffee generally contains between 50-100mg of caffeine, although some studies have reported amounts ranged between 51 and 322mg per cup in different types of

commercialized *espresso*.[3] Contrary to what the name might suggest, decaffeinated coffee also contains caffeine however, in lesser quantities (0.8 to 1.7mg/100ml).[1]

Caffeine exerts a variety of different actions in humans, most of which can be explained by structural similarities to the adenosine molecule. Such similarities allow caffeine to act as a competitive inhibitor of G-protein-coupled A_1 and A_2 adenosine receptors (AR), exerting stimulating effects on the central nervous system mainly through the blockade of adenosine's predominant inhibitory action.[4] In the heart, adenosine's actions are mainly mediated by receptors A_1, A_3, A_{2A} and A_{2B}.[21] **(Figure 2)** The AR system can affect all major components of cardiovascular function not only through multiple interactions between receptor sub-types but also other G-protein-coupled receptors.[22]

As a consequence of adenosine receptor blockade, caffeine leads to an increase in plasma adenosine concentration. In turn, raised adenosine levels stimulate arterial chemoreceptors, giving rise to a variety of systemic effects such as the increase in sympathetic tone, circulating catecholamines, peripheral vascular resistance and renin secretion. [23]

Other mechanisms by which caffeine exerts its actions involve direct effects on the vascular endothelium, through mobilization of intracellular calcium via ryanodine channels in the endoplasmic reticulum and consequent nitric oxide (NO) production. Caffeine is capable of elevating cyclic adenosine monophosphate (cAMP) levels in smooth muscle cells through inhibition of phosphodiesterase activity.[23] In cardiac muscle, increase in cAMP results in positive inotropic action. [24] Despite its different actions **(Figure 3)**, it is the interaction between caffeine and adenosine receptors that is thought to mediate the main cardiovascular effects, since the latter mechanisms seem to require higher and even toxic levels of intracellular caffeine concentration (higher than the ones obtained by moderate coffee intake). [4, 23]

Many papers outline variable susceptibility to the actions of caffeine. Seeing as caffeine is metabolized in the liver, these variations have been attributed to differences in genetic polymorphisms, induction or inhibition of cytochrome P450, CYP1A2, responsible for caffeine metabolization, as well as individual variables of weight, sex and presence of

hepatic disease. [3, 4, 10] In fact, in a genome-wide meta-analysis, involving 47341 patients, an association between caffeine consumption, CYP1A2 and the aryl hydrocarbon receptor (which regulates the CYP1A2 activity) genes was demonstrated.[25] Genetic determinants of such a behavioural trait may aid future understanding of the beneficial and toxic effects of caffeine amongst different individuals.

Coffee's effects on hemodynamics and the sympathetic nervous system have always classically been attributed to caffeine. However, similar increases in blood pressure and sympathetic nerve activity have been reported after the ingestion of both caffeinated and decaffeinated coffee in non-habitual coffee drinkers, suggesting that components other than caffeine might also be responsible for coffee's stimulating effects on the cardiovascular system. [26]

Chlorogenic Acids

Coffee contains several phenolic compounds with recognized antioxidant capacity.[27, 28] The most abundant phenolic compounds identified in coffee are CGAs, a family of esters formed between hydroxycinnamic acids (which consist of mostly caffeic and ferulic acid) and quinic acid. Up to 95% of CGA content in green coffee beans is lost during the roasting process. Even so, coffee is possibly the richest dietary source of CGAs and its content in an *espresso* can range from 24 to 423mg.[3, 10]

CGAs have been suggested to modulate the expression of genes involved in endogenous antioxidant defence mechanisms, implying a possible protective role against diseases with an inflammatory basis. [3, 10] Additionally, CGAs have been implied in arterial blood pressure (BP) control. Hypertension is one of the major contributors to the development of HF through multiple mechanisms, including NO-mediated endothelial dysfunction, via imbalance between NO and superoxide production. [29] Possible association between oxidative stress and blood pressure has been noted in experimental studies. In this context, actions through which CGAs are thought to regulate BP possibly include inhibition of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Inhibition of this enzyme is thought to result in decreased free radical production, increased endothelial-mediated NO production and inhibition of angiotensin-converting enzyme (ECA).[30]

Together with caffeine[31], CGAs have been held partly responsible for the higher homocysteine concentrations reported in habitual coffee drinkers. [32] Homocysteine is considered a minor clinical risk factor for HF.[8] However, it is unclear if the elevation of homocysteine levels by CGAs translates an increase in cardiovascular disease risk**.**

Diterpenes

Kahweol and cafestol are the main diterpenes present in coffee. Concentrations of these compounds highly depend upon brewing technique and can range from 0.6-12mg per cup. [3, 10] Scandinavian boiled coffee is seen to contain high concentrations of diterpenes. Filter coffee contains minor amounts of diterpenes, as does instant coffee, since the filtration process can remove most diterpene containing oils from the mixture. [17] *Espresso* coffee has been reported to contain high concentrations of kahweol and cafestol, however, due to its habitual small serving size, it is not considered a major source of diterpenes.[3]

Through multiple cell-specific mechanisms involved in the cholesterol metabolism and reduction of the LDL receptor activity, kahweol and cafestol have been held mainly responsible for the serum lipid raising effect of coffee. [10, 17] The increase in total cholesterol observed with these compounds is mainly due to increases in LDL and VLDL cholesterol and decrease in HDL cholesterol. A proposed explanation for these effects implies the increased activity of cholesteryl ester transfer protein (CEPT) brought about by diterpene compounds.[4]

On the other hand, diterpenes have also been seen to exert beneficial effects on human health by enhancing endogenous defensive mechanisms against oxidative damage.[3]

Melanoidins

Melanoidins are high molecular weight nitrogenous brown coloured polymers that are thought to act as dietary fibre. These components are formed during the roasting process of coffee and are responsible for the drink's pleasant flavour. Coffee is one of the main sources of this compound in the human diet. [3, 10] Much is yet to be discovered regarding the chemistry of melanoidins, since their complex and unstable chemical structure makes them difficult to isolate. [33]

Antioxidant and anti-inflammatory effects have been recorded with melanoidins, both *in vivo* and *in vitro.* Suggested mechanisms for such observations include free radical scavenging activity and metal-chelating capacity.[10]

Potential antihypertensive properties have been reported with high molecular weight material obtained by ultrafiltration of instant coffee, where melanoidins were assumed to be part of the filtrate. Although such properties have only been reported *in vitro*, possible inhibition of ACE (a zinc dependant enzyme) due to melanoidin's metal chelating properties has been proposed.[10] However, there is no evidence that melanoidins are absorbed intact into the circulatory system[3], raising the question whether or not these findings are significant *in vivo.*

HEART FAILURE

Whichever the cause, HF may be described as the inability of the heart to maintain an adequate cardiac output, in order to guarantee the organism's metabolic requirements.[34] Systolic or diastolic left ventricular dysfunction are considered precursors of HF and occur in asymptomatic patients. [5] In over 50% of patients with left ventricular systolic dysfunction (LVSD), signs or symptoms of HF are absent.[7]

Heart failure may affect both left and right ventricles and the dysfunction may be predominantly systolic, diastolic or both.[34] According to current classification, HF patients can be divided based on their ejection fraction: preserved (≥50%), mid-range (40-49%) or reduced (<40%).[5]

Due to it's massive global impact on healthcare, HF has been described as a global pandemic and public health burden.[35] Although incidence and prevalence of HF seems to be lower in women at any age, due the increased life expectancy of the female population, the total number of men and women with HF remains similar.[36] Patient characteristics appear to differ among patients with different HF types. Heart failure with reduced ejection fraction (HFrEF) mainly occurs in men with a history of myocardial infarction, whereas patients with

heart failure with preserved ejection fraction (HFpEF) are usually older women with a history of hypertension and atrial fibrillation (AF).[5]

In Portugal, the prevalence of chronic HF estimated by the EPICA study is 4.36‰, just slightly above what has been reported by other European studies. [37]

Increased activation of the sympathetic and renin-angiotensin-aldosterone system (RAAS) are key points in the pathophysiology of HF. Additionally, inflammatory action also seems to play a part in HF. [34]

EPIDEMIOLOGY: COFFEE AND RISK OF HEART FAILURE

It is safe to say that coffee is part of most, if not all, modern civilizations. In the meanwhile, as previously discussed, the prevalence of HF is globally significant. Based on frequent association between common lifestyle habits and cardiovascular health, many epidemiological studies have attempted to determine the relationship between coffee intake and the risk cardiovascular disease, including HF.

In the past, elevated coffee consumption has been considered a risk factor for HF. In fact, in an epidemiological study, a multivariate analysis performed amongst 6570 men aged 47-55 showed that coffee consumption ≥5 cups/day was a risk factor for HF.[6] Nevertheless, no mention of the type of coffee preparation method utilized was made in this study, making it impossible to exclude the consumption of unfiltered or boiled coffee, which has been found to be deleterious to cardiovascular health through the elevation of serum lipids. [17]

On the other hand, in 2011, a prospective observational study performed with 34551 women aged 48 to 83 from the Swedish Mammography Cohort study showed no evidence to support that the daily consumption of ≥5 cups of coffee (as opposed to < 5 cups per day) increased the rate of HF, postulating that intake of coffee is not an important risk factor for the development of HF. [38] Similar conclusions were reached in a prospective cohort study with 48850 participants aged 45 to 79, from the Cohort of Swedish Men. [39] Both studies refer possible misclassification regarding exposure to coffee consumption through applied questionnaires. Also, both study populations were drawn from Sweden, which might limit

the generalization of these studies to other populations with different coffee consumption routines.

Coffee consumption did not increase HF risk in prospective population-based cohort study of Finnish men and women. In fact, in this study, Wang *et al.* observed an inverse association between low to moderate coffee consumption (1 to 6 cups daily) in women only. Authors suggest that gender disparities observed may be related to different prevalence of smoking and, therefore, smoking-related unhealthy lifestyles between sexes.[40]

In a case-control study, coffee consumption decreased the likelihood of developing LVSD in normotensive, post-acute coronary artery event survivors and increased likelihood of developing such dysfunction in hypertensive patients.[29] This suggested that, for some unclear reason, coffee exerted opposite effects depending on patient's baseline blood pressure levels.

In 2012, a systematic review and dose-response meta-analysis of 5 prospective studies demonstrated a J-shaped relationship between moderate coffee consumption and the risk of HF, having the strongest inverse association been shown with 4 cups/day (11% lower risk). (**Figure 4)** Most of the studies included in the analysis were restricted to people with no myocardial infarction or diabetes at baseline. This adjustment is particularly relevant due to the fact that coffee is commonly believed to be deleterious to the heart, hence people with particular health conditions may tend to reduce their average coffee consumption.[41]

In 2014 a meta-analysis of 36 studies with a prospective design by Ming Ding et al, demonstrated a non-linear association between coffee consumption and cardiovascular disease (CVD) risk (coronary heart disease, stroke, HF, CV mortality). Three to five cups/day were seen to be associated with a lower risk of CVD.[9] Also, contrarily to previous findings [6], in this study heavy coffee consumption (≥6cups/day) did not alter the risk of CVD.[9]

An analysis of the data from the National Health and Nutrition Examination Survey did not show impact of stratified average daily coffee consumption on all cause-mortality nor cause-

specific mortality. Based on their findings, authors even suggest protective effects of coffee on cardiac ischemia-related mortality.[12]

All in all, most of the above studies have concluded that no association between coffee consumption and risk of HF may be found, with some even suggesting possible inverse association between both variables [9, 40, 41]. It is relevant to refer that the majority of these studies point out no differentiation between coffee types and brewing methods as a limitation. Lack of stratification while collecting information on dietary habits poses an important limitation to epidemiological investigation.

Some authors suggest that coffee consumption may differently influence HF with preserved versus reduced ejection fraction, or even that of ischemic versus non-ischemic cause.[39] To evaluate this, further characterization of HF would be required.

Additionally, to purposefully evaluate the risk of developing HF, selected patients in these studies did not have HF at baseline, making it difficult to extrapolate these findings to a population with pre-established HF in order to evaluate the safety of coffee consumption and possible effect on HF prognosis.

COFFEE AND MECHANISMS OF ADAPTIVE RESPONSE IN HEART FAILURE

Neurohumoral Activation

Particularly in early stages of HF, neurohumoral activation plays a fundamental role in the compensation of a progressive decrease in mean arterial blood pressure. In attempt to maintain an adequate cardiac output, stimulation of the sympathetic nervous system and consequent release of catecholamines leads to both direct effects on the heart and peripheral vasculature. Also in response to decreased mean arterial blood pressure, the RAAS induces vasoconstriction of peripheral vasculature and sodium retention.[34]

Caffeine has been found to influence the RAAS axis in individuals with elevated renin, such as those suffering from HF.[23] Evidence suggests that caffeine is capable of augmenting renin secretion through the blockade of adenosine's inhibitory effects on the kidney's juxtaglomerular cells, via A_1 receptor.[42] Through either caffeine mediated phosphodiesterase

inhibition or sympathetic activation, increased cAMP levels also stimulate the release of renin.[23, 43] Nevertheless, caffeine's effects on renin release stimulation have not been consistent.[44, 45]

It has been hypothesised that methylxantines such as caffeine are capable of modulating the vascular response to angiotensin II, via adenosine receptor blockade. Oral administration of caffeine has been seen to result in a reduction of the vasoconstrictor response to adenosine in the renal circulation.[45] Nevertheless, the relevance of these finings remains questionable.

Other substances present in coffee also interact with the RAAS. The previously discussed CGA are capable of inhibition of the ACE, both *in vivo* and *in vitro*[30] and this is also thought to be true for melanoidins.[10] Angiotensin-converting enzyme inhibitors (ACEIs) are recommended for the treatment of patients with both asymptomatic LVSD and HFrEF for they have been shown to reduce risk of progression and improve survival in HF.[5] Since both ACEIs and CGA act upon a common molecular target, one may speculate that CGAs may be beneficial in HF.

Plasma norepinephrine, angiotensin II and inflammatory cytokines augmented in HF promote the transcription of the enzyme responsible for adenosine production, ecto-5'-nucleotidase. As expected, adenosine levels are elevated in the blood plasma of patients with HF.[22, 46] The action of adenosine on receptor A_1 leads to the inhibition of norepinephrine release from cardiac nerves. Such inhibition is thought to protect the heart from excessive activation during periods of increased sympathetic activity such as HF.[22] Hence, augmented adenosine production by endothelial cells and cardiomyocytes may be regarded as a mechanism to counteract deleterious effects of increasing catecholamine levels in failing heart.[46] This compensatory mechanism may be impaired by caffeine through AR blockade, explaining why caffeine seems to facilitate norepinephrine release and increased sympathetic tone. However, clinical data to support whether or not this mechanism is significant in HF is lacking.

Endothelial Response

Endothelial dysfunction plays an important role in the progression and prognosis of HF. The loss in vasodilator properties appears to be systemic, particularly in HF of ischaemic aetiology. [47]

By using flow-mediated dilation in the brachial artery to quantify endothelial dysfunction, Papamichael *et al.* demonstrated that ingestion of a cup of instant coffee (containing 80mg of caffeine) in healthy subjects acutely impaired endothelial-mediated vasodilation whereas the same was not verified with decaffeinated coffee.[48] In a similar study, authors reported favourable dose-dependant effects on the endothelial function after ingestion of decaffeinated coffee, with significant increase in flow-mediated vasodilation. These results suggest that substances in coffee other than caffeine such CGA antioxidant may be responsible for the observed improvement in endothelial function.[49]

In fact, CGA's have demonstrated antioxidant properties, capable of improving endothelial and vascular function through the increased availability of NO.[50] Ferulic acid in particular was seen to increase NO bioavailability and endothelial-dependant vasodilation in arterial vasculature.[30] However there is limited evidence on the implications of such effect on individuals with established endothelial dysfunction.

Inflammatory Signalling and Ventricular Remodelling

Inflammation has been found to take part in the pathophysiology of HF.[34] Either as determinants of increased risk of HF, in the case of several pro-inflammatory cytokines and C-reactive protein[8], or as prognostic markers in the case of tumour necrosis factor (TNF) and its soluble TNF-receptors 1 and 2[51], mediators of inflammation are of unquestionable relevance in cardiac failure.

Numerous adenosine receptors present in the heart are involved in different processes, including that of inflammatory regulation.[22] Therefore, it is not surprising that methylxanthines such as caffeine have been seen capable of immunomodulatory activity.[52]

NADPH oxidase, augmented in the HF [53], is outlined as a possible source of increased reactive oxygen species (ROS) production in the failing myocardium. [51] Consequently, this excessive NADPH oxidase activation may be a potential treatment target for preventing cardiomyocyte hypertrophy and damage in HF.[51] CGAs, the main phenolic compounds present in coffee, are capable of inhibiting NADPH oxidase as well as direct scavenging of free radicals. [30]

Through the inhibition of angiotensin II formation, ACEIs beneficially influence vascular inflammatory processes, prevent smooth muscle proliferation and activation of the vascular and phagocytic NADPH oxidase from superoxide formation. [54] Thus, in theory it is possible that CGA's inhibitory action of the ACE may also contribute to its potential anti-inflammatory effect.

With disease progression, continuous neuro-humoral activation in HF eventually leads to ventricular remodelling with further myocardial dysfunction.[34] Oxidative stress directly influences cardiac remodelling through increase in ROS production and decreased antioxidant defence systems.[55]

Pro-inflammatory factors TNF-α and IL-6, along with angiotensin II and catecholamines, all elevated in HF, are responsible for maladaptive remodelling, hypertrophy, and consequent cardiac fibrosis and cell apoptosis.[51] All AR sub-types are capable of anti-hypertrophic and anti-remodelling actions. Therefore, modifications in AR expression and function may contribute to contractile dysfunction and remodelling in HF.[22, 56] In this sense, adenosine modulation, which influences TNF-alfa and IL-6 expression, may prevent maladaptive remodelling. [22]

In the past, CGAs have been tested on cardiomyocyte hypertrophy induced by isoproterenol, a synthetic catecholamine. The observed increase in ROS by isoproterenol in this study was attenuated by CGAs through their presumed ROS scavenging ability. [57]

Although targeting inflammatory signalling seems promising, attempted scavenging of ROS through molecules with antioxidant activity has not shown to be effective in modifying

prognosis of HF patients. Thus, more studies are required to identify specific targets on a cellular level.[54]

EFFECT OF COFFEE ON HEART FAILURE MORBIDITY

Arrhythmia

The most common type of arrhythmia observed in patients with HF is AF.[5] Particularly when control over ventricular rate is absent, AF may lead to HF. In advanced stages, HF may also trigger AF, leading to a vicious cycle in which neuro-humoral activation plays an important role. [6]

In the past, acute induction of cardiac arrhythmias with caffeine has been suggested, after exposure to caffeine in the presence of norepinephrine was seen to induce positive inotropy and triggered automaticity on human ventricular muscle fibres from transplanted HF patients. Such findings have been attributed to a possible consequence of intracellular calcium overloading.[24] Thus, this synergism between caffeine and norepinephrine has been suggested as the basis of supposed arrhythmogenic properties of caffeine in advanced HF.

Nevertheless, recent studies have challenged the common belief that coffee consumption is arrhythmogenic, suggesting neutral or even beneficial relationship between coffee and arrhythmia.[50] Furthermore, electrophysiological studies have not proven association between caffeine and malignant ventricular arrhythmia.[28]

In a large Scandinavian prospective cohort study sought to investigate whether daily consumption of caffeine was associated with increased risk of atrial flutter or AF, no association was observed. In this study, caffeine consumption was evaluated with a semi-quantitative food-frequency questionnaire applied on 47 949 participants from the Danish Diet, Cancer, and Health Study. Coffee was identified as the main source of caffeine, due to patterns of both high coffee caffeine content and high coffee consumption in Denmark. [58]

Ten years later, using the same cohort, the association between risk of AF and coffee consumption was evaluated, under the rationale that coffee contains more than just caffeine, thus the health effects of this mixture of compounds may differ from those

observed with caffeine alone. After adjusting for confounders, a statistically significant linear trend showed higher levels of coffee consumption to be associated with a lower rate of incident AF.[59]

Premature ventricular complexes are detected in almost every patient with HF and asymptomatic, non-sustained ventricular tachycardia is common, particularly as ventricular dysfunction progresses[5]. More recently, a randomized control trial tested high dose caffeine ingestion (500mg) versus placebo on 51 patients with chronic HF due to systolic dysfunction at high risk of ventricular arrhythmia. Based on the premature ventricular and supraventricular beats observed in both groups, authors did not find evidence to support common recommendation to restrict caffeine consumption in patients at risk of arrhythmia. As a limitation of the applied methodology, the study was not able to ensure that applied caffeine doses were not associated with long-term pro-arrhythmic effects in HF. [60]

Although it is intuitive to recommend caffeine reduction in patients at risk of arrhythmia, it is also accepted that patients should only be advised to stop consuming coffee if they exhibit major symptoms (palpitations, anxiety, tremors, nausea, trouble sleeping and headaches) after intake. [4, 61]

Exercise Tolerance

Exercise tolerance is an important clinical marker in HF patients, for whom exercise is generally limited by symptoms.[5]

In a study designed to evaluate the effect of caffeine (infused in a dose equivalent to 2 cups of coffee) on exercise duration and tolerance on HF patients (NYHA classes I to III), increased duration to peak effort was seen, despite increase in minute ventilation. Amongst potential explanations for these findings authors suggest reduced muscle metaboreflex-induced vasoconstriction, positive inotropic action, potential analgesic effects on muscle fatigue at peak exercise and improved neuromuscular functions[62]. In fact, augmented muscle metaboreflex-induced vasoconstriction in patients with HF is connected to diminished exercise tolerance.[63] Adenosine was recognised as a stimulus to this exaggerated post-

exercise vasoconstrictor effect. For this reason, AR (particularly A_1 and A_2) inhibition by caffeine was capable of abolishing this effect, improving exercise tolerance in HF. [64]

Congestive Symptoms

Fluid overload is responsible for congestive symptoms observed in HF. For this reason, diuretics are recommended in selected patients with HFrEF.[5] Although effects on morbidity and mortality are unclear, diuretics are seen to lessen symptoms and increase exercise capacity. Diuretic action attributed to caffeine has been described in doses similar to those obtained by intake of 2 to 3 cups of coffee.[65] Caffeine is thought to enhance the effect of diuretics, hence improving the condition of patients with HF. [50]

CONCLUSION

Variable effects of coffee intake among individuals are the result of different consumption patterns and polymorphisms involved in the metabolism of caffeine. Adverse effects on serum lipids are more related with unfiltered coffee. Within low to moderate levels of coffee intake (<6 cups/day), available evidence regarding the effect of coffee on cardiovascular disease risk, trends towards a neutral or even beneficial effect on blood pressure and diabetes mellitus. Consumption of 3 to 4 cups a day appears to decrease risk of HF. In similar doses, evidence suggests that coffee may play a role in alleviating HF symptoms. Contrary to general belief, coffee does not seem to trigger arrhythmia in HF patients with systolic dysfunction. Potential theoretical adverse effects on blood pressure and peripheral vascular resistance due to caffeine seem to be counteracted by CGA polyphenols and other compounds with antioxidant capacity. Few studies however address the safety of coffee consumption in patients with pre-established HF. In light of current knowledge, low to moderate coffee consumption does not seem to be harmful in HF.

FIGURES

Figure 1 – Schematic representation of both possible and verified effects of coffee and its individual components on cardiovascular parameters and potential risk factors. Effects marked with a * are obtained through the antagonism of adenosine receptors.

Figure 2 – Adenosine receptor cell signalling. Representation of the similarities between adenosine and caffeine molecules.

Figure 3 - Caffeine's main mechanisms of action on endothelial cells, smooth muscle cells and cardiomyocytes.
(A) In levels equivalent to that those obtained through moderate coffee consumption caffeine's main mechanism of action if through the blockade of adenosine receptors in various tissues.
(B) On endothelial cells, caffeine acts directly by stimulating ryanodine receptors in the endoplasmic reticulum, leading to a release of Ca2+ and consequent increase in levels of Ca2+ in the cytoplasm. Elevation Ca2+ levels will lead to calcium-calmodulin complex formation, activating nitric oxide (NO) synthase and consequent production of NO. In turn, NO diffuses and exerts vasodilatation on vascular smooth muscle cells.
(C) On vascular smooth muscle cells, caffeine is capable of phosphodiesterase inhibition, leading to accumulation of cAMP with consequent reduction of Ca2+ in the cytoplasm as well as inhibition of the Myosine Light Chain Kinase (MLCK) enzyme and consequent activation of Myosin Light Chain Phosphatase (MLCP) in the cell's contractile apparatus. This results in reduced actin-myosin interaction, relaxation and consequent vasodilation.
(D) The effect of phosphodiesterase inhibition and increased cAMP levels on cardiomyocytes leads to increased activity of PKA, phospholaban inhibition through phosphorylation, consequent increased sarcoplasmic reticulum Ca2+ATPase (SERCA) and positive inotropic action on the myocardium.

Figure 4 – Relative Risk (solid line) and 95% confidence interval (dashed line) for the association between heart failure and cups of coffee per day, compared to no consumption in a meta-analysis of studies published from 2001 through 2011. **A.** Primary analysis

including all 5 studies analyzed. **B.** Analysis after exclusion of a study that did not adjust for any potential confounders. Reproduced with permission from *Mostofsky E, Rice MS, Levitan EB, Mittleman MA. Habitual coffee consumption and risk of heart failure: a dose-response meta-analysis. Circulation Heart failure. 2012* [41]

Figure 1.

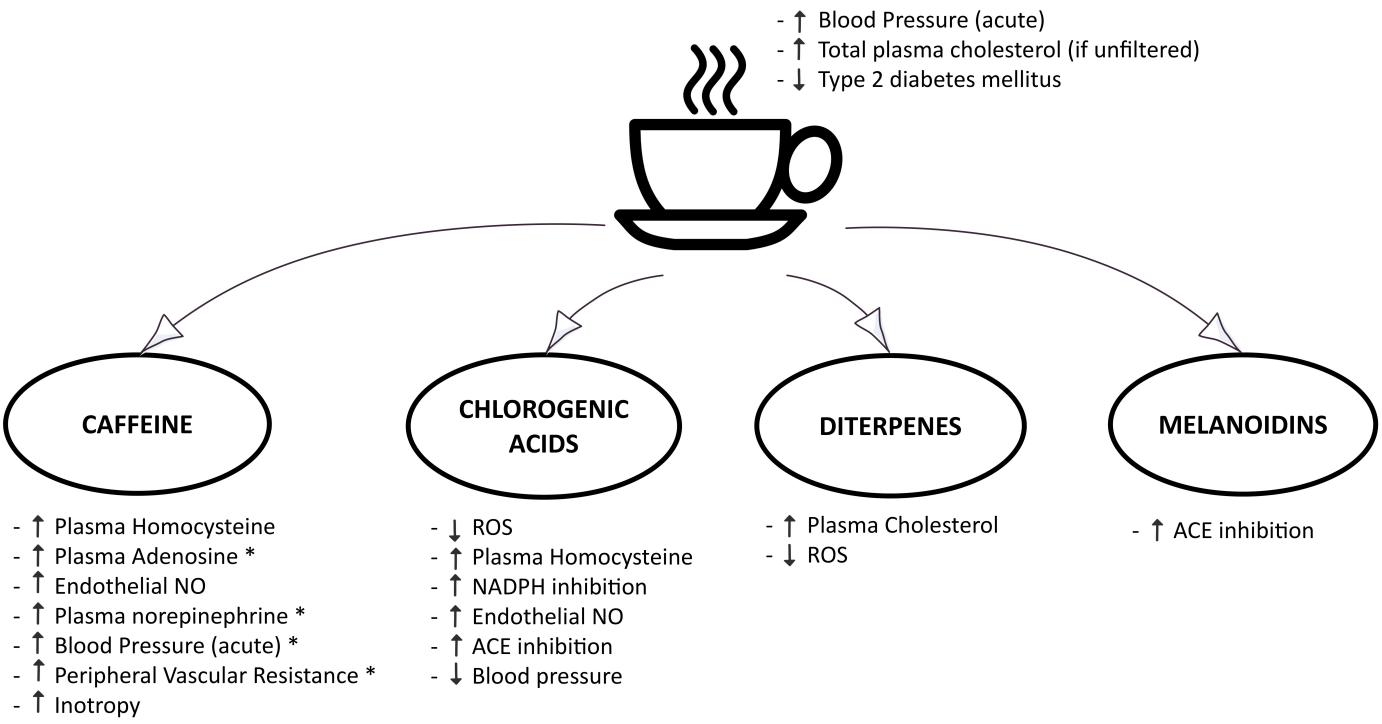

- ↑ Blood Pressure (acute)
- ↑ Total plasma cholesterol (if unfiltered)
- ↓ Type 2 diabetes mellitus
CAFFEINE
- ↑ Plasma Homocysteine
- ↑ Plasma Adenosine *
- ↑ Endothelial NO
- ↑ Plasma norepinephrine *
- ↑ Blood Pressure (acute) *
- ↑ Peripheral Vascular Resistance *
- ↑ Inotropy
CHLOROGENIC ACIDS
- ↓ ROS
- ↑ Plasma Homocysteine
- ↑ NADPH inhibition
- ↑ Endothelial NO
- ↑ ACE inhibition
- ↓ Blood pressure
DITERPENES
- ↑ Plasma Cholesterol
- ↓ ROS
MELANOIDINS
- ↑ ACE inhibition

Figure 2.

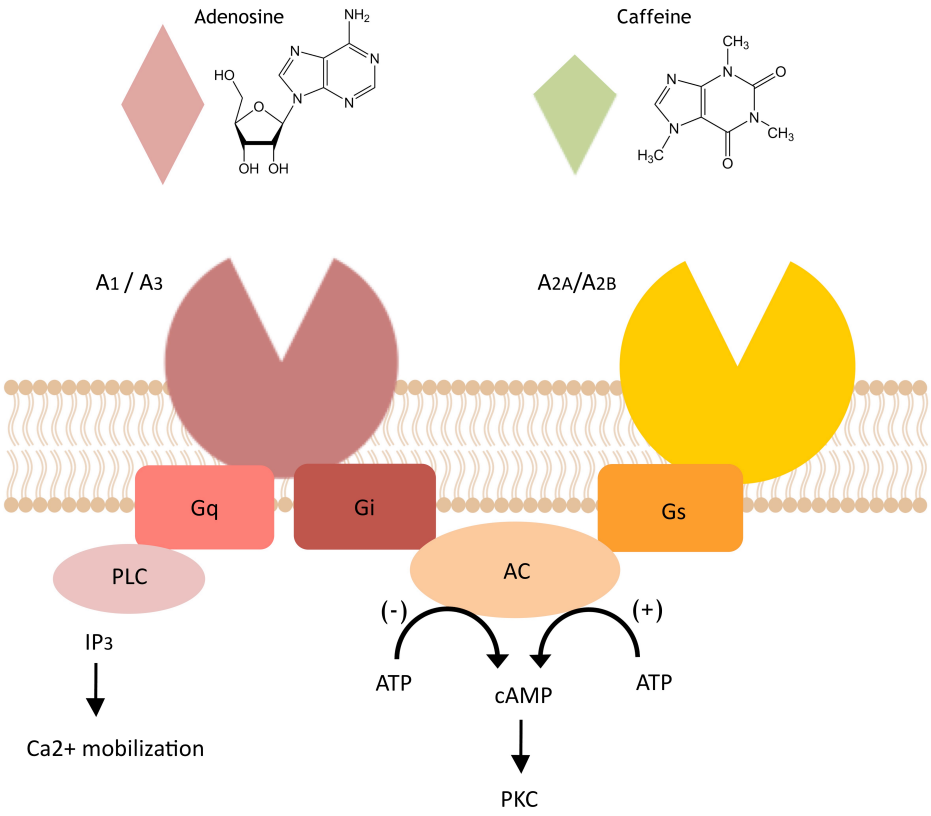
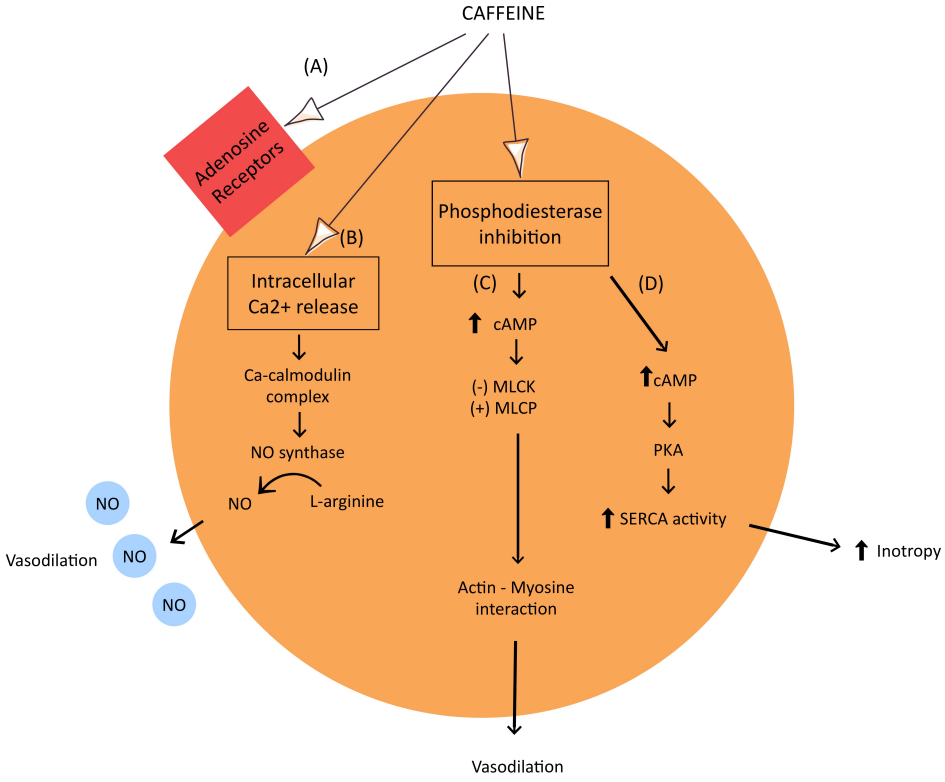
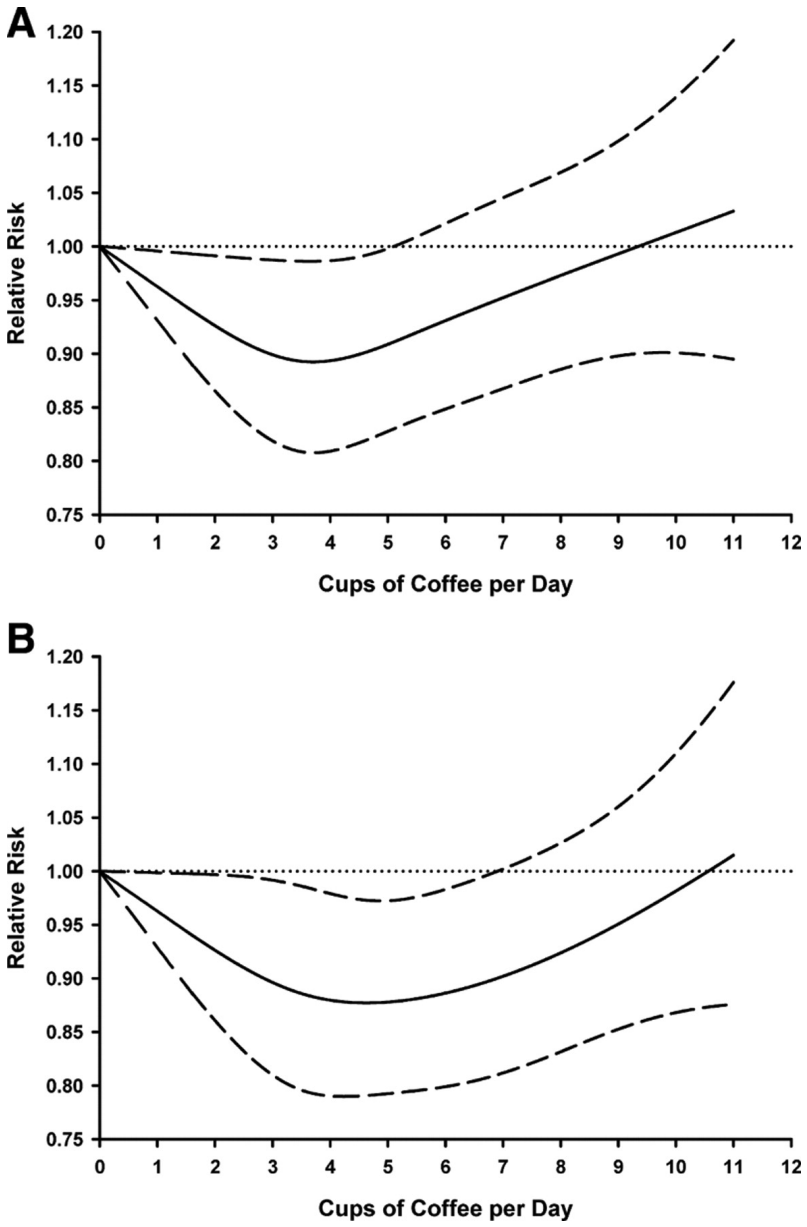

Adenosine
Caffeine
A1 / A3
A2A/A2B
Gq
Gi
Gs
PLC
AC
IP3
(-)
(+)
ATP
cAMP
ATP
Ca2+ mobilization
PKC

Figure 3.



Endothelial cell / Smooth muscle cell / Cardiomyocyte

Figure 4.


A
Relative Risk
1.20
1.15
1.10
1.05
1.00
0.95
0.90
0.85
0.80
0.75
0 1 2 3 4 5 6 7 8 9 10 11 12
Cups of Coffee per Day
B
Relative Risk
1.20
1.15
1.10
1.05
1.00
0.95
0.90
0.85
0.80
0.75
0 1 2 3 4 5 6 7 8 9 10 11 12
Cups of Coffee per Day

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Anexos

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Título completo (menos de 150 caracteres) em português e em inglês.

Nome e apelido dos autores pela ordem seguinte: nome próprio, seguido do apelido (pode conter dois nomes)

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Deverá ser elucidativo e não inclui referências bibliográficas nem abreviaturas (excepto as referentes a unidades de medida).

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Texto

Deverá conter as seguintes partes devidamente assinaladas: *a)* Introdução; *b)* Métodos; *c)* Resultados; *d)* Discussão e e*)* Conclusões. Poderá utilizar subdivisões adequadamente para organizar cada uma das secções.

As abreviaturas das unidades de medida são as recomendadas pela RPC (ver Anexo II).

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Revista médica: Lista de todos os autores. Se o número de autores for superior a três, incluem-se os três primeiros, seguidos da abreviatura latina et al. Exemplo:

17. Sousa PJ, Gonçalves PA, Marques H et al. Radiação na AngioTC cardíaca; preditores de maior dose utilizada e sua redução ao longo do tempo. Rev Port cardiol, 2010; 29:1655-65

Capítulo em livro: Autores, título do capítulo, editores, título do livro, cidade, editora e páginas. Exemplo:

23. Nabel EG, Nabel GJ. Gene therapy for cardiovascular disease. En: Haber E, editor. Molecular cardiovascular medicine. New York: Scientific American 1995. P79-96.

Livro: Cite as páginas específicas. Exemplo:

30. Cohn PF. Silent myocardial ischemia and infarction. 3rd ed. New York: Mansel Dekker; 1993. P. 33.

Material electrónico: Artigo de revista em formato electrónico. *Exemplo:*

Abood S. Quality improvement initiative in nursing homes: the ANA acts it an advisory role. Am J Nurs. [serie na internet.] 2002 Jun citado 12 Ago 2002:102(6): [aprox. 3] p. Disponível em: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

. A Bibliografia será enviada como texto regular, nunca como nota de rodapé. Não se aceitam códigos específicos dos programas de gestão bibliográfica.

1. Figuras

As figuras correspondentes a gráficos e desenhos são enviadas no formato TIFF ou JPEG de preferência, com uma resolução nunca inferior a 300 dpi e utilizando o negro para linhas e texto. São alvo de numeração árabe de acordo com a ordem de entrada no texto.

- A grafia, símbolos, letras, etc, deverão ser enviados num tamanho que, ao ser reduzido, os mantenha claramente legíveis. Os detalhes especiais deverão ser assinalados com setas contrastantes com a figura.
- As legendas das figuras devem ser incluídas numa folha aparte. No final devem ser identificadas as abreviaturas empregues por ordem alfabética.
- As figuras não podem incluir dados que dêem a conhecer a proveniência do trabalho ou a identidade do paciente. As fotografias das pessoas devem ser feitas de maneira que estas não sejam identificadas ou incluir-se-á o consentimento por parte da pessoa fotografada.

Tabelas

São identificadas com numeração árabe de acordo com a ordem de entrada no texto.

Cada tabela será escrita a espaço duplo numa folha aparte.

- Incluem um título na parte superior e na parte inferior são referidas as abreviaturas por ordem alfabética.
- O seu conteúdo é auto-explicativo e os dados que incluem não figuram no texto nem nas figuras.

2. Artigos de Revisão

N° máximo de palavras do artigo sem contar com o resumo e quadros- 5.000
N° máximo de palavras do Resumo - 250
N° máximo de Figuras - 10
N° máximo de quadros - 10
N° máximo de ref. bibliográficas - 100

3. Cartas ao Editor

Devem ser enviadas sob esta rubrica e referem-se a artigos publicados na Revista. Serão somente consideradas as cartas recebidas no prazo de oito semanas após a publicação do artigo em questão.

- Com espaço duplo, com margens de 2,5 cm.
- O título (em português e em inglês), os autores (máximo quatro), proveniência, endereço e figuras devem ser especificados de acordo com as normas anteriormente referidas para os artigos originais.
- Não podem exceder as 800 palavras.
- Podem incluir um número máximo de duas figuras. As tabelas estão excluídas.

4. Casos Clínicos

Devem ser enviados sob esta rubrica.

- A espaço duplo com margens de 2,5 cm.
- O título (em português e em inglês) não deve exceder 10 palavras

Os autores (máximo oito) proveniência, endereço e figuras serão especificados de acordo com as normas anteriormente referidas para os artigos originais.

O texto explicativo não pode exceder 3.000 palavras e contem informação de maior relevância. Todos os símbolos que possam constar nas imagens serão adequadamente explicados no texto.

Contêm um número máximo de 4 figuras e pode ser enviado material suplementar, como por exemplo vídeoclips.

5. Imagens em Cardiologia

- A espaço duplo com margens de 2,5 cm.
- O título (em português e em inglês) não deve exceder oito palavras
- Os autores (máximo seis), proveniência, endereço e figuras serão especificados de acordo com as normas anteriormente referidas para os artigos originais.
- O texto explicativo não pode exceder as 250 palavras e contem informação de maior relevância, sem referências bibliográficas. Todos os símbolos que possam constar nas imagens serão adequadamente explicados no texto.
- Contêm um número máximo de quatro figuras.

6. Material adicional na WEB

A Revista Portuguesa de Cardiologia aceita o envio de material electrónico adicional para apoiar e melhorar a apresentação da sua investigação científica. Contudo, unicamente se considerará para publicação o material electrónico adicional directamente relacionado com o conteúdo do artigo e a sua aceitação final dependerá do critério do Editor. O material adicional aceite não será traduzido e publicar-se-á electronicamente no formato da sua recepção.

Para assegurar que o material tenha o formato apropriado recomendamos o seguinte:

	Formato	Extensão	Detalhes
Texto	Word	.doc ou docx	Tamanho máximo 300 Kb
Imagem	TIFF	.tif	Tamanho máximo 10MB
Audio	MP3	.mp3	Tamanho máximo 10MB
Vídeo	WMV	.wmv	Tamanho máximo 30MB

Os autores deverão submeter o material no formato electrónico através do EES como arquivo multimédia juntamente com o artigo e conceber um título conciso e descritivo para cada arquivo.

Do mesmo modo, este tipo de material deverá cumprir também todos os requisitos e responsabilidades éticas gerais descritas nessas normas.

O Corpo Redactorial reserva-se o direito de recusar o material electrónico que não julgue apropriado.

ANEXO I

DECLARAÇÃO

Declaro que autorizo a publicação do manuscrito:

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Título .....

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do qual sou autor ou c/autor.

Declaro ainda que presente manuscrito é original, não foi objecto de qualquer outro tipo de publicação e cedo a inteira propriedade à Revista Portuguesa de Cardiologia, ficando a sua reprodução, no todo ou em parte, dependente de prévia autorização dos editores.

Nome dos autores:

.....

.....

Assinaturas:

ANEXO II

Símbolos, abreviaturas de medidas ou estatística

Designação	Português	Inglês
Ampere	A	A
Ano	ano	yr
Centímetro quadrado	cm_2	cm_2
Contagens por minuto	cpm	cpm
Contagens por segundo	cps	cps
Curie	Ci	Ci
Electrocardiograma	ECG	ECG
Equivalente	Eq	Eq
Grau Celsius	°C	°C
Grama	g	g
Hemoglobina	Hb	Hb
Hertz	Hz	Hz
Hora	h	h
Joule	J	J
Litro	L ou L	l ou L
Metro	m	m
Minuto	min	min
Molar	M	M
Mole	mol	mol
Normal (concentração)	N	N
Ohm	Ω	Ω
Osmol	osmol	osmol
Peso	peso	WT
Pressão parcial de CO_2	pCO_2	pCO_2
Pressão parcial de O_2	pO_2	pO_2
Quilograma	kg	kg
Segundo	s	sec
Semana	Sem	Wk
Sistema nervoso central	SNC	CNS
Unidade Internacional	UI	IU
Volt	V	V
Milivolt	mV	mV
Volume	Vol	Vol
Watts	W	W
Estatística:		
Coeficiente de correlação	r	r
Desvio padrão (standard)	DP	SD
Erro padrão (standard) da média	EPM	SEM
Graus de liberdade	gl	df
Média	χ	χ
Não significativa	NS	NS
Número de observações	n	n
Probabilidade	p	p
Teste «t» de Student	teste t	t test