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Metabolic effects of cardiovascular drugs

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ABSTRACT

Prescription of cardiovascular drugs is aimed at preventing and treating morbid conditions affecting the cardiovascular system. However, apart from their primary therapeutic target, some of the ordinary drugs used in cardiology daily practice also have additional pharmacological actions. Among these ancillary actions, those primarily affecting global and cardiac metabolism deserve special attention. In fact, apart from primary cardiac metabolic diseases, most cardiovascular diseases are heavily influenced by the patient's metabolic status and adaptation to the disease itself. In this context, drugs affecting global and cardiovascular metabolism besides their recognized main mechanism of action may be of special interest, for both potential beneficial and deleterious effects, especially in the long-term period. In all cases, these effects should be well understood and known by all physicians managing patients with cardiovascular morbidities. The aim of this article is to describe the direct metabolic actions of some of the principal cardiovascular drugs.

Introduction

Prescription of cardiovascular drugs is aimed at preventing and treating morbid conditions affecting the cardiovascular system. Their mode of action is usually directed towards the pathophysiological mechanisms of the underlying disease. For instance, anti-anginal drugs are used to reduce oxygen consumption or increase oxygen supply; in heart failure, drug therapy is directed towards interrupting neuro-hormonal activation; in arrhythmia control, drugs are used for their cellular electrophysiological effect. However, apart from their primary therapeutic target, some of the ordinary drugs used in cardiology daily practice also have additional pharmacological actions. Among these ancillary actions, those primarily affecting global and cardiac metabolism deserve special attention [1]. In fact, apart from primary cardiac metabolic diseases, most cardiovascular diseases are heavily influenced by the patient's metabolic status and adaptation to the disease itself. In this context, drugs affecting global and cardiovascular metabolism, in addition to their recognized main mechanism of action, may be of special interest for both potential beneficial and deleterious effects. In all cases, these effects should be well understood and known by all physicians managing patients with cardiovascular morbidities.

The aim of this article is to describe the often unknown metabolic properties of some of the principal cardiovascular drugs. The most important drug-induced secondary metabolic changes will also be mentioned. In fact, drug-induced vasodilatation, unloading of the heart, heart rate reduction and ventricular function improvement, singularly and all together contribute to cardiac, and often global, metabolism improvement. Positive and negative effects on cardiac and global metabolism will be reported. The choice of one drug within a given pharmacological class could potentially be more effectively directed by taking into consideration these ancillary effects.

The term metabolism has a wide significance and therefore, in the present review, we will mainly address the effects on intermediary energy metabolism. Table 1 shows a rapid summary of the main metabolic effects of the drugs evaluated in the present review.

Aspirin

Aspirin irreversibly inhibits cyclo-oxygenases and thus blocks platelet aggregation. Apart from its principal antithrombotic therapeutic effect, it has also been shown to reduce circulating free fatty

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Table 1
Main metabolic effects of drugs frequently employed in cardiac patients.

Drug	Metabolic effects
Acetylsalicylic acid	• Reduction of circulating FFA, by activating AMP-activated protein kinase • Activation of catabolic pathways (glucose uptake and FFA oxidation) • NF-kB inhibition (increased insulin sensitivity)
Beta Blockers	• Reduction of peripheral lipolysis • Reduction of circulating levels of FFA • Increased carbohydrates utilization • Improved insulin sensitivity (carvedilol)
Ivabradine	• Reduced mitochondrial reactive oxygen species formation, increased ATP production and calcium retention capacity
CCBs	• Reduce myocardial carbohydrates utilization
Nitrates	• Increase the lipid to carbohydrates oxidation ratio
Alpha-blockers	• Improved glucose metabolism mediated by improved endothelial vasomotor function and reversed abnormal arteriolar structure • Direct inhibitory effect on cholesterol synthesis independent of the LDL receptor
Central sympathetic inhibitors	• Reduction of FFA • Improved insulin secretion • Potential direct cholesterol-reducing effect • However, in heart failure moxonidine increases FFA utilization and myocardial oxigen consumption
RAAS inhibitors	• Improved glucose homeostasis by increased blood flow in skeletal muscle, accumulation of bradykinin or more efficient insulin release
Thiazide diuretics	• Induced hyperlipidemia • Induced insulin resistance • Induced hypokaliemia and hyperuricemia • Increased risk of metabolic syndrome • positive bone homeostatic effect
MRAs	• Detrimental effects on glucose and lipid homeostasis by increased cortisol levels through blockade of the glucocorticoid receptors • However, eplerenone appears devoid of metabolic effects
Amiodarone	• Inhibition of mitochondrial fatty acid oxidation • Inhibition of plamitoyltransferase-1 • Increased cholesterol serum concentrations by reduction of LDL receptor
Heparin	• Increased circulating FFA by release of endothelial and hepatic lipoprotein lipase, thereby promoting hydrolysis of triacylglycerol in chylomicrons and very-low-density lipoprotein • At high doses, NO production impairment
DTIs	• Increased peripheral lipolysis
Statins	• Pravastatin promotes risk reduction for new onset of diabetes (and other statins including atorvastatin, rosuvastatin and simvastatin showing significant increase in this risk) • All statins reduce testosterone serum concentrations
Trimetazidine	• Selective block of long chain 3-KAT activity, the last enzyme involved in beta-oxidation • Reduction of FFA oxidation • Enhancement of insulin sensitivity • Improved glycolysis and glucose oxidation
Ranolazine	• Modulation of late sodium current, thereby reducing the accumulation of intracellular Ca^{++} • Increased glucose oxidation
L-Carnitine/ Mildronate	• L-carnitine increases glucose oxidation despite elevated FFA serum concentrations but potentially exerts negative effects on cardiovascular risk through increases in trimethylamine-N-oxide production (promoting atherosclerotic lesion development) • Mildronate inhibits fatty acids oxidation and activates glycolysis

CCBs: calcium channel blockers; DTIs: direct thrombin inhibitors; FFA: free fatty acids; KAT: ketoacyl-coenzyme-A thiolase; LDL: low-density lipoproteins; MRAs: mineral corticoid receptor antagonists; NF-kB: nuclear factor-kB; NO: nitric oxide; RAAS: renin-angiotensin-aldosterone system; TG: triacylglycerols

acids and/or triacylglycerols [2]. These changes in lipid metabolism are consistent with the reported inhibitory effects of salicylates on peripheral lipolysis [3] and liver fatty acid synthesis [4]. These metabolic effects can potentially be explained by the recent observation that aspirin may directly activate AMP-activated protein kinase (AMPK) [5]. AMPK is a key regulator of metabolism: its activation determines the phosphorylation of numerous metabolic enzymes, acutely decreasing anabolic pathways that consume ATP, such as fatty acid, triacylglycerol, phospholipid, and protein biosynthesis, while activating catabolic pathways that generate ATP, such as glucose uptake and fatty acid oxidation (for review see [6]. Aspirin has also been shown to inhibit activation of the transcription factor NF-κB [7] by preventing degradation of IKK-β, which regulates the inflammatory responses, and might therefore ameliorate insulin resistance and improve glucose tolerance. More recently, aspirin has been shown to improve glucose tolerance in

aspirin-treated rats, due a combination of its anti-inflammatory properties and enhanced nitric oxide levels that facilitates insulin signaling and energy utilization in target tissues [8]. On these grounds, apart from its primary anti-platelet adhesion effect, the therapeutic use of aspirin in insulin-resistant conditions could be envisaged.

Beta blockers

This class of drugs targets the beta receptors. Beta adrenergic blocking agents are prescribed for the management of patients with various clinical manifestations of heart disease. Increases in the sympathetic outflow to the heart have been shown to precipitate ischemia and to predispose underperfused myocardium to its development. Increased sympathetic stimulation of the cardiovascular system increases tachycardia, hypertension and increased contractility, with all these conditions being well known to increase myocardial energy metabolic requirements. Therefore, the fact that the latter agents have been proposed as first line drugs for the treatment of myocardial ischemia is not surprising. In fact, beta blockers blunt the cardiovascular response to adrenergic stimulation, thus reducing ischemia and protecting the infarcted myocardium. Beta blockers have also been shown to directly affect myocardial energetics, independently from their effects on cardiac mechanics [9]. In addition, among the mechanisms promoting lipolysis, stimulation of the beta1 receptor located on adipose tissue is prominent. Thus beta-blockade, by reducing peripheral lipolysis, results in a reduction in circulating levels of free fatty acids (FFA) and induces a shift of heart energy metabolism towards a greater utilization of carbohydrates due to substrate competition [10]. These biochemical events have been held responsible for the reduction in myocardial FFA uptake [11], as well as for the increase in glucose utilization [12] induced by beta blockers. When ischemia is induced by pacing in patients with obstructive coronary artery disease, beta blockers decrease arterial FFA concentrations and increase cardiac lactate extraction [13]. The observed increase in cardiac carbohydrate metabolism after beta-blockade probably results from decreased FFA delivery as well as from augmented arterial glutamate availability [14, 15]. The latter may be a particularly useful substrate, especially during myocardial ischemia, as it can be utilized as an anaerobic as well as an aerobic fuel [15]. Therefore, a higher rate of carbohydrate utilization induced by beta blockade may result in a greater cardiac energy production at similar levels of oxygen consumption. Thus, in addition to their well known hemodynamic effects, beta blockers may also be effective by primarily acting on metabolic aspects of myocardial ischemia and, possibly, heart failure. This change in myocardial energetics could provide a potential mechanism for the decreased myocardial oxygen consumption and improved energy efficiency seen with beta blockade in the treatment of ischemic heart disease and heart failure [16]. In patients with heart failure the magnitude of heart rate reduction could therefore be just a marker of a better functional response following beta blocker administration, a consequent effect rather than a mechanism [17].

In fact, lowering raised plasma triacylgycerols and FFA serum concentrations could be the first therapeutic option to decrease the failing heart's reliance on fatty acids and overcome the fatty acid inhibition of myocardial glucose utilization. Indeed beta blockers, by reducing peripheral lipolysis, do reduce FFA availability. Interestingly, two studies have shown that the beta blocker carvedilol reduces FFA utilization in favor of greater glucose utilization in patients with stable NYHA functional class III heart failure [18] This change in myocardial energetics could provide a potential mechanism for the decreased myocardial oxygen consumption and improved energy efficiency seen with beta blockade in the treatment of heart failure. It appears that non selective, compared to selective, beta blockers are more efficient in shifting total body energy substrate utilization from lipid to glucose oxidation [19]. Nevertheless, better metabolic effects of the former could be one of the reasons of better survival rates observed with their use [20].

Finally, beta blockers have been also shown to interfere with blood lipid serum concentrations, by increasing triacylglycerol serum concentrations up to 40% and decreasing high density lipoprotein cholesterol serum concentrations by approximately 20% [21]. These alterations in lipoprotein serum concentrations from beta blockers are not a class effect. In fact, non-selective beta blockers that cause peripheral vasoconstriction through peripheral β-adrenergic receptors seem to increase insulin resistance, leading to lowering of HDL-C, and increased triacylglycerol serum concentrations [22]. On the contrary, cardioselective agents and those with vasodilating properties do not appear to increase insulin resistance. Carvedilol has selective $\alpha-1$-adrenoreceptor blocking activity, causing vasodilation and a reduction in insulin resistance. Additionally, the superiority of carvedilol compared to metoprolol and atenolol on lipid parameters has been demonstrated in small studies [22,23]. Similarly, nebivolol, another vasodilating beta blocker, has been shown to yield a neutral effect on the lipid profile [24].

Ivabradine

Heart rate is an important determinant of myocardial metabolism. A considerable body of evidence indicates that elevated resting heart rate is an independent, modifiable risk factor for cardiovascular events and mortality. Myocardial cellular energy reserve in healthy young adult men is inversely associated with heart rate [25], which is an important determinant of cardiac energy consumption. For these reasons, pharmacologically induced heart rate reduction may have a role in preserving myocytes energy levels. Ivabradine, a relatively recently developed drug, acts by reducing the heart rate via specific inhibition of the funny (I_f) current, a mechanism different from that of beta blockers and calcium channel blockers. It has been shown that mere heart rate reduction by ivabradine selectively reduces heart rate while preserving energy substrate metabolism of normoxic healthy working mouse hearts perfused ex vivo [26]. In a mouse model of dyslipidemia with preserved cardiac hemodynamics, ivabradine, but not metoprolol, despite similar heart rate reductions, preserved cardiac function and glucose metabolism during disease progression [27]. Despite ivabradine reducing heart rate by inhibiting I_f current in the sinus node [28], there are also ivabradine targets in ventricular cardiomyocytes. The I_f channels are members of the hyperpolarization-activated cyclic nucleotide gated (HCN) channel family, and HCN4 is the main isoform expressed in the sinus node of the heart [29]. However, HCN2 and 4 have also been demonstrated in ventricular myocardium of mice [30] and humans, particularly in failing human hearts [31]. In fact, in another animal study, ivabradine reduced infarct size independently of a reduction in heart rate and improved ventricular cardiomyocyte viability, possibly by reducing mitochondrial reactive oxygen species formation, increasing ATP production and calcium retention capacity [32]. Whether or not heart rate-independent metabolic cardioprotection mediated by ivabradine was induced by HCN inhibition in ventricular cardiomyocytes or some other action is unclear from this study and deserves further investigation.

Calcium channel blockers

These drugs block calcium inward currents triggered by various stimuli and are potent dilators of coronary and peripheral arteries. However, the peripheral arterial vasodilatation caused by calcium antagonists, may induce reflex adrenergic activation and consequent vasoconstriction and tachycardia. Therefore, the net hemodynamic and electrophysiological effect of these drugs results from a complex interplay of both direct and reflex phenomena. Structurally, there are three types of calcium entry blockers: the phenylalkylamines, the benzothiazepines and the dihydropyridines, all interacting with specific binding sites at the cellular level. Calcium currents play a major role in several fundamental physiological processes of the myocardial and smooth muscle cells. Apart from their specific cardiac hemodynamic and electrophysiological effects, they may also influence myocardial energetics [33]. Cardiac lactate extraction increases during myocardial ischemia after the administration of calcium antagonists [34]. Calcium channel blockers have also been shown to decrease lactate extraction in lactate non-producers during pacing [35], suggesting that these drugs may inhibit myocardial carbohydrate utilization. In support of this, it has been shown that diltiazem decreases glycolysis in rat hearts, thereby decreasing lactate production and improving the coupling of glycolysis to glucose oxidation [36]. A higher FFA/carbohydrate utilization ratio induced by calcium blockers during stress may be determined by their ability to influence glucose transport across the cell membrane and by intracellular calcium release [35]. In fact, the hormonal regulation of glucose metabolism is regulated by a complex hormonal interplay, which involves catecholamines, insulin, glucagon, thyroid hormones and acetylcholine. Cyclic adenosine 3′,5′-monophosphate, a second messenger for intracellular signal transduction, stimulates myocardial glucose uptake which is partly mediated by increased Ca^{2+} transients [37]. As intracellular calcium is a stimulus for glucose uptake, calcium channel blockers have been shown to suppress physiological myocardial glucose uptake [38]. However, despite the perceived overall beneficial effects of these drugs in patients with different cardiac conditions, whether the primary effects of these drugs on coronary hemodynamics exceed those secondary to myocardial metabolic effects is not yet clear, at least in patients with existing metabolic derangements. Three randomized trials and supportive data from several observational studies have documented an excess risk of cardiovascular events associated with the use of dihydropyridine calcium channel blockers compared with other agents among hypertensive patients with diabetes or pre-diabetes [39]. Additionally, in the ALLHAT trial, fasting glucose serum concentrations increased in older hypertensive adults regardless of treatment type (chlorthalidone, lisinopril, amlodipine) [40]. For those taking chlorthalidone vs other medications, the risk of increased fasting glucose serum concentrations was modestly greater [41]. However, despite a less favorable metabolic profile, thiazide-like diuretic evidenced a superior cardiovascular outcome [42]. On this ground, further studies are necessary to evaluate the exact metabolic role of different classes of calcium channel blockers in cardiac patients, especially in subgroups of patients with metabolic disorders.

Nitrates

The role of nitrates on cardiac energy metabolism is not fully understood and it is likely to be indirect. Some studies have suggested that nitrates increase the lipid to carbohydrates oxidation ratio, possibly by optimizing energy utilization mainly via cardiac unloading [33]. Indeed, the beneficial effects of nitrates on exercise-induced ischemia are definitely more pronounced when these drugs are given systemically rather than locally, by the intracoronary route [43]. Furthermore, nitroglycerin does not affect the metabolism or performance of the isolated rat heart, as long as heart rate, preload and afterload are kept constant [44]. Taken together, all these observations strongly suggest that organic nitrates have no direct effect on cardiac energy metabolism. Whether more subtle intracellular changes are induced by these compounds remains to be elucidated.

Nicorandil (*N*-[2-hydroxyethyl] nicotinamide nitrate) has 2 main mechanisms of action: a cyclic guanosine monophosphate (GMP)-dependent component as a nitrate [45] and an adenosine triphosphate (ATP)-sensitive $K^+(K_{ATP})$ channel-dependent component as a K_{ATP} channel opener [46]. However, it is unclear which component is predominant. Potassium channel openers protect cardiac mitochondria by attenuating oxidant stress at re-oxygenation. Suppression of excessive reactive oxygen species production induced by potassium channel openers preserves electron transport, maintains mitochondrial oxidative phosphorylation, and prevents cytochrome c release, indicating a generalized protection of mitochondria from anoxia-re-oxygenation injury [47]. However, data obtained in a previous experimental study suggest that nicorandil may even aggravate the metabolic and energetic situation of ischemic myocardium [48]. The influence of the drugs on the metabolism of glucose, lactate and free fatty acids (FFA) were examined under basic conditions, in ischemia and during reperfusion. Under basic conditions, glucose metabolism was significantly enhanced in both groups, but FFA metabolism was inhibited only by isosorbide dinitrate. In ischemia, FFA metabolism was enhanced by nicorandil and depressed by isosorbide dinitrate. Taken together, these results suggest that nicorandil may even aggravate the metabolic and energetic situation of ischemic myocardium; on the other hand, the results support a potential protective metabolic effect of nitrates [48]. The beneficial metabolic actions of nicorandil may instead occur during reperfusion and may be the result of a reduction in oxygen free radical production [49].

Alpha-adrenergic blockers

Alpha-adrenoceptor antagonists (also called alpha blockers) cause vasodilation by blocking the binding of norepinephrine to the smooth muscle receptors. Alpha blockers are mainly used for treating hypertension, usually in association with other drugs. Prazosin, terazosin and doxazosin are relatively selective alpha 1-adrenoceptor antagonists, whereas older drugs are non-selective antagonists (phentolamine, phenoxybenzamine). Non selective drugs, by blocking pre-junctional alpha 2-adrenoceptors, can lead to increased release of norepinephrine, which can partly attenuate the effectiveness of the alpha1 and alpha2-postjunctional adrenoceptor blockade and can lead to increases in heart rate and contractility. Additionally, small increases in plasma epinephrine serum concentrations could increase hyperglycemia through stimulation of both glycogenolysis and gluconeogenesis, resulting in a potential negative metabolic profile of these drugs [50].

On the other hand, selective alpha-1 blocking agents have been shown to yield a beneficial effect on glucose and lipid profiles [51,52]. It is likely that the observed beneficial glucose metabolism effects are mediated by improved endothelial vasomotor function and reversed abnormal arteriolar structure [53]. However, increased insulin secretion by a mechanism not involving alpha 2-adrenergic receptors directly has been implicated as a possible mechanism of alpha blockers induced glucose metabolism improvement in normal subjects or patients with non insulin-dependent diabetes [54].

Additionally, alpha blockers may have a direct inhibitory effect on cholesterol synthesis independent of the LDL receptor. The in-

hibition of cholesterol synthesis may cause cells to compensate by up-regulating the LDL receptor, thereby increasing the importation of lipoprotein cholesterol and reducing LDL cholesterol [55]. On the other hand, in an experimental study doxazosin suppressed the accumulation of cholesterol and the formation of atherosclerotic plaques in aortas of rabbits and prevented a diet-induced increase in aortic collagen and wall mass without altering serum concentrations of cholesterol, triacylglycerol, glucose, free fatty acid or ketone levels [56]. These results indicate a possible involvement of alpha 1-adrenergic receptors in the recruitment of smooth muscle cells by sub-intimal macrophages and non-adrenergic mechanisms of inhibition of lipid infiltration. Overall, despite the lack of significant evidence in randomized clinical studies, doxazosin associated changes in insulin and lipid metabolism could eventually contribute to decrease the risk of coronary heart disease in patients with mild hypertension.

Central sympathetic inhibitors

Many disease states are accompanied by chronic elevations in sympathetic nerve activity. An overactive sympathetic nervous system is present in many cardiovascular diseases including ischemic heart disease, chronic heart failure, and hypertension. Protecting the heart from sympathetic overactivity by beta blockers has proven to be beneficial for survival in hypertensive and heart failure patients and therefore, as previously outlined, beta blockers have become a mainstay of therapy in these conditions. However, a more effective therapeutic approach may be to inhibit central sympathetic outflow directly by stimulating $\alpha 2$ or imidazoline receptors in the central nervous system. Clonidine ($\alpha 2$ and imidazoline receptor agonist) and moxonidine (selective imidazoline receptor agonist) effectively reduce sympathetic nervous activity. Chronic inhibition of sympathetic activity with moxonidine therapy has been shown to lower FFAs and significantly improve insulin secretion, glucose disposal, and expression of key insulin signaling intermediates in an animal model of obese hypertension [57]. A therapeutic role for moxonidine has also been hypothesized for chronic heart failure patients. However, central inhibition of sympathetic nervous activity with moxonidine in heart failure has been associated with increased mortality [58]. In fact, despite a significant reduction of cathecolamine spillover and, consequently, a decreased heart rate, in chronic heart failure moxonidine has been shown to increase FFA utilization and increase myocardial oxygen consumption [59]. This could be the reason for the failure of central sympathetic inhibition to prevent deaths in long term studies in patients with heart failure and also indicates that the predominant mechanism of action of beta blockers in heart failure and other cardiac conditions is probably related to mechanisms of action other than simple heart rate reduction [17].

Finally, central sympathetic outflow inhibition may also have effects on lipid profiles. In fact, there is some evidence that moxonidine can improve atherogenic lipid and lipoprotein profiles [60] by increased insulin-sensitisation and possibly through a direct cholesterol-reducing effect [61].

Renin–angiotensin–aldosterone system (RAAS) inhibitors

The renin–angiotensin system (RAS) or the renin–angiotensin–aldosterone system (RAAS) is a hormone system that regulates blood pressure and fluid balance. Angiotensin II is also an important regulator of cardiac energy metabolism and function. There are several mechanisms through which angiotensin II may directly contribute to cardiac dysfunction occurrence and persistence [62]. Angiotensin II damages mitochondria in the cardiomyocyte by increasing reactive oxygen species production [63] and affects mitochondrial oxidative phosphorylation, including fatty acid oxidation [64]. These data suggest that angiotensin II affects fatty acid oxidation. There is also evidence that angiotensin II regulates glucose oxidation [65] and that inhibition of angiotensin II effects may exert beneficial effects. In addition, by decreasing oxidative metabolism, angiotensin II can reduce ATP levels, thus compromising ATP production [66]. In this context, angiotensin II antagonism represents an attractive therapeutic approach. Studies using the euglycaemic insulin clamp technique have indicated that the beneficial effect of angiotensin II antagonism is exerted on insulin sensitivity. In fact, angiotensin-converting enzyme (ACE) inhibitors [67] and angiotensin receptor antagonists [68] have been shown to improve both left ventricular function and glucose homeostasis. Increased blood flow in skeletal muscle, accumulation of bradykinin or more efficient insulin release have been suggested as potential modes of action.

Angiotensis receptor neprilysin inhibitors (ARNI)

Compared with the angiotensin-converting enzyme inhibitor (ACEI) enalapril, sacubitril/valsartan (formerly known as LCZ696), an angiotensin receptor-neprilysin inhibitor (ARNI), improved morbidity and mortality in patients with heart failure and reduced ejection fraction in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial, after a median follow-up of 27 months [69]. Sacubitril/valsartan did not reduce the pre-specified exploratory outcome of new onset diabetes in comparison with enalapril, although the number of patients with new-onset diabetes during the course of the trial was very small. However, sacubitril/valsartan has been shown to improve glucose metabolism in patients with heart failure and diabetes [70].

Thiazide and loop diuretics

Antihypertensive drugs should correct small artery structure and impaired endothelial function [71]. In fact, the degree of remodelling predicts events in hypertensive subjects and endothelial dysfunction results from the oxidative stress that may also predict events: correction of small artery structure and function may favorably affect outcomes in hypertension. Thiazide diuretics are extensively used to treat hypertensive subjects, despite the fact that they also may cause a number of vascular and metabolic abnormalities that increase cardiovascular risk, including endothelial dysfunction and vascular oxidative stress [72], hyperlipidemia [73], insulin resistance [74], new onset diabetes mellitus [75], hypokalemia [76], hyperuricemia [77] and stimulation of the sympathetic [78] and RAAS pathways [79]. In the ALLHAT study, for example, a significant increase in the development of type 2 diabetes was observed in thiazide-treated patients compared with other treatment groups (11% versus 9.3% and 7.8%, for 4-year incidence in chlorthalidone, amlodipine and lisinopril groups, respectively [80]. Some have argued that these metabolic effects did not translate into a greater frequency of cardiovascular events, and that thiazides as initial therapy for hypertension offer possibly superior cardiovascular disease outcomes in older hypertensive adults even with the metabolic syndrome, as compared with treatment with calcium channel blockers and ACE-Inhibitors. If one also considers, however, that antihypertensive management is usually life-long, that hypertension and metabolic syndrome are rampant and that increasing numbers of adolescents are developing obesity and hypertension, then one must be concerned about the long-term consequences of thiazide therapy. Indeed, it has been clearly shown that diuretics are not endowed with pleiotropic vasoprotective ef-

fects beyond lowering blood pressure. Even when administered in association with an ACE-Inhibitor, thiazide diuretics abolish the anti-atherosclerotic effect of the latter [81]. The long-term effects of thiazide diuretic therapy on glucose metabolism and consequent adverse cardiovascular, cerebrovascular and renal effects will take longer to manifest than the relatively short duration of clinical studies. Therefore, if thiazide diuretics provoke new-onset diabetes, the adverse cardiovascular consequences would not be apparent in a study of 3–5 years duration.

It also appears that hyperuricemia and hypokalemia may have pivotal roles in the exacerbation of the metabolic syndrome in response to thiazides, increasing the risk for metabolic syndrome or diabetes. A strong relationship between hypokalemia and glucose intolerance has been observed in a quantitative review of 59 thiazide diuretic clinical trials [82]. The results clearly suggest that treatment of thiazide-induced hypokalemia could lessen glucose intolerance and possibly the development of diabetes. However, no prospective clinical trials have reported the development of diabetes as a function of potassium serum concentrations.

Apart from energy metabolism, diuretics have been shown to have significant effects on bone mineral density and fracture risk. Thiazide diuretics can affect kidney, intestine, and bone and thereby modulate calcium homeostasis. In the kidney, thiazides inhibit the thiazide-sensitive sodium chloride co-transporter in the distal tubule and exert natriuretic and calcium-sparing effects. In the intestine, thiazides enhance calcium uptake and suppress parathyroid hormone secretion. Overall, thiazides reduce urinary excretion of calcium by about 40% [83]. Additionally, thiazides exert direct effects on bone by stimulating osteoblast differentiation and bone mineral formation through osteoblast differentiation markers [84]. These mechanisms could explain why, independent of their renal and intestinal effects, thiazides are able to exert a direct positive homeostatic effect on bones. Through these mechanisms, thiazide diuretics increase (or prevent decreases) in bone mineral density in both men and women and, in observational studies, are associated with a reduction in fracture risk [83].

Loop diuretics increase the urinary excretion of sodium chloride by selective inhibition of the sodium, potassium and chloride co-transporters in the loop of Henle and distal nephron. Loop diuretics promote sodium and water excretion via the kidney and mitigate excessive sodium and water retention. Treatment with loop diuretics is associated with significantly increased urinary calcium excretion, and increased serum concentrations of PTH and 1,25-dihydroxyvitamin D [85]. Long-term treatment with furosemide causes hypocalcaemia, resulting in elevation of PTH and increased serum concentrations of bone specific alkaline phosphatase, an indication of accelerated bone remodeling [86].

Mineralocorticoid receptor antagonists (MRAs)

MRAs, such as spironolactone and eplerenone, block the deleterious effects of aldosterone that are mediated by the mineralocorticoid receptor. Consequently, this pharmacological activity makes MRAs effective in treating hypertension, particularly resistant hypertension, and in reducing the risk of morbidity and mortality in heart failure patients. It has been repeatedly observed that “off-target effects” of spironolactone could also include detrimental effects on glucose and lipid homeostasis [87]. A potential cause of this negative effect is the fact that spironolactone increases cortisol serum concentrations through an off-target effect: the blockade of the glucocorticoid receptors. Cortisol, a glucocorticoid, increases glucose through increasing lipolysis and gluconeogenesis. On the other hand, eplerenone, a selective MRA, has a very low activity on other steroid receptors. As such, it does not inhibit adrenal cell aldosterone or cortisol production and does not affect glucose metabolism [88]. A recent systematic review of randomized controlled trials, prospective and observational studies evaluating the influence of the different MRAs on biomarkers of glucose homeostasis in a variety of populations, has indeed confirmed that spironolactone may induce alterations in glycemia, while eplerenone does not have an impact on glucose homeostasis [89]. In fact, eplerenone had no effect on new-onset diabetes in patients with chronic heart failure enrolled in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure study (EMPHASIS-HF) [90].

Amiodarone and antiarrhythmic drugs

Amiodarone is a class III anti-arrhythmic drug that has been shown to prolong action potential duration and the refractory period. It was first utilized as an anti-ischemic agent due to its vasodilating properties. Apart from these effects and its well known potential side effects on the thyroid gland (it can induce both hypo- and hyper-thyroidism due to its high iodine content), amiodarone has been shown to induce direct cellular metabolic effects. These may explain its anti-ischemic actions, which were the original target therapeutic indications when the drug was first synthesized. In particular, it has been shown that it can determine hepatic steatosis from an accumulation of triacylglycerols in hepatocytes [91]. In fact, amiodarone is lipophilic and can easily cross the mitochondrial outer membrane. It also inhibits mitochondrial carnitine palmitoyltransferase-1 (CPT-1) located on the outer mitochondrial membrane [92], similar to what is observed with etomoxir, perhexiline and oxfenicine. The progressive accumulation of the drug inside the mitochondria may result in a progressive decline in cellular respiration and a decrease of mitochondrial beta-oxidation of fatty acids, with a consequent markedly decreased ATP formation in mouse liver mitochondria [93]. Therefore, amiodarone, apart from its present therapeutic indication as an antiarrhythmic agent, also yields important metabolic actions that could be of primary importance in determining its anti-ischemic effect. However, whether these effects eventually translate into improved LV function and prognosis is not established.

Amiodarone has also been shown to increase plasma cholesterol serum concentrations in a dose-dependent manner [94]. Apart from potential amiodarone-induced thyroid hormone deficiency, this effect is due in part to a decrease in the number of LDL receptors [95].

Dronedarone is a noniodinated benzofuran derivative of amiodarone developed for the treatment of atrial fibrillation and a potent blocker of multiple ion currents. However, animal studies indicate that dronedarone also can induce dyslipidemia and these effects may be associated with thyroid dysfunction [96]

Sotalol is a non-selective competitive beta blocker that also exhibits Class III antiarrhythmic properties (amiodarone like). Sotalol in association with hydrochlorotiazide has been compared with an association of hydrochlorotiazide and ACE-inhibitor [97]. Both associations were shown to exert adverse effects on lipid and glucose metabolism after long-term therapy. However, diuretic/beta blocker combinations had a greater impact on lipid and glucose metabolism after long-term therapy. The effects of the diuretic/ACE inhibitor combination on lipid metabolism were less pronounced and there were no adverse effects on glucose metabolism. However, the ACE inhibitor component could not completely counteract the detrimental metabolic effects of the diuretic [97]. In fact, it is likely that the negative additive metabolic effects of sotalol could be ascribed to the metabolic pharmacological combined proper-

ties of the beta blockade and amiodarone-like components of this drug.

As for four other widely used antiarrhythmic drugs, digoxin, dofetilide, propafenone and flecainide, no significant metabolic effects associated with their use have been reported.

Heparin

Unfractionated heparin binds to the enzyme inhibitor antithrombin III (AT) and activates it. Activated AT then indirectly inactivates thrombin and other proteases involved in blood clotting, most notably activated factor X (Xa). Despite these beneficial effects, its administration also increases circulating FFAs [98], which may adversely affect myocardial energetics, especially during ischemia [99]. Additionally, high-dose heparin, at concentrations often achieved in acute cardiovascular conditions, could increase platelet aggregation [100], and impair NO production and vasomotion in rats [101]. These observations suggest that high doses of heparin, by interfering with the production of NO, can exert pro-thrombotic effects and negatively affect myocardial perfusion.

In the past, standard unfractionated heparin has been shown to reduce the ischemic threshold in patients with coronary artery disease (CAD), probably by increasing FFA release [102]. Heparin administration causes the release of endothelial and hepatic lipoprotein lipase (LPL), thereby promoting hydrolysis of triacylglycerol in chylomicrons and very-low-density lipoprotein into two nonesterified fatty acids (NEFAs) and monoacylglycerol [103]. This may further worsen the metabolic milieu of the ischemic myocardium. Exogenous fatty acids, the main metabolic fuel of the myocardium under aerobic conditions, are detrimental under oxygen deprivation, because their presence decreases glucose metabolism and further augments the accumulation of long-chain acyl esters in myocytes. The accumulation of lipids and their degradation may contribute to the progression of injury.

Similar to unfractionated heparin, direct thrombin inhibition has been shown to enhance peripheral lipolysis [104]. Direct thrombin inhibitors (DTI) have been associated with a greater risk of myocardial infarction [105]. A recent meta-analysis performed on 39,357 patients demonstrated that oral administration of DTI, compared with warfarin, was associated with increased risk of MI [106]. If this were the case, beside other mechanisms, in patients on therapy with DTI high serum concentrations of circulating FFA could facilitate the occurrence of myocardial necrosis in the setting of acute coronary syndromes. Further studies are definitely necessary to clear out the doubts on the use of these drugs in the general population and, more specifically, in patients with coronary artery disease [107].

Statins

3–hydroxy–3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are a class of drugs that lowers cholesterol by inhibiting HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. Statins are a mainstay therapy in most cardiovascular diseases. The relation between endothelial dysfunction and insulin resistance suggests that therapies improving endothelial dysfunction will simultaneously improve insulin sensitivity and other metabolic parameters. However, despite significant statin-induced improvement in endothelial function and decreases in circulating pro-inflammatory markers, previous reports indicated that statins either do not alter insulin sensitivity or may actually promote insulin resistance [108]. This may be due to pleiotropic or “off-target effects” of some statins to cause insulin resistance by diverse mechanisms unrelated to endothelial dysfunction. Indeed, there is evidence of other differential metabolic actions of distinct statins including effects on HMG-CoA reductase inhibition, isoprotenoid synthesis, calcium release, glucose transport, insulin secretion, and/or insulin resistance. Overall, statin therapy is associated with a slightly increased risk of diabetes development, but the risk is low both in absolute terms and when compared with the reduction in coronary events [109]. Nevertheless, clinical studies demonstrate potential differences between individual statins, with pravastatin promoting risk reduction for new onset of diabetes [110] and other statins including atorvastatin [111], rosuvastatin [112] and simvastatin [108] showing significant increase in this risk. As for diuretics, the long-term effects of statins on glucose metabolism and consequent adverse cardiovascular effects will take longer to manifest than the relatively short duration of clinical studies. In fact, the adverse cardiovascular effects of diabetes take 10–15 years to manifest and the risk of statin-associated diabetes mellitus could, in fact, minimize or eliminate the beneficial effects of those drugs over a longer time period.

Cholesterol is the principal compound of all steroid hormones, including testosterone and estrogens. Statins, by reducing cholesterol serum concentrations, may impact the capacity of steroidogenic tissues to produce adrenocortical hormones and sex steroids. In fact, a recent meta-analysis of placebo-controlled randomized trials suggests that statins reduce testosterone [113]. Additionally, the magnitude of the decrease in testosterone has been shown to be directly proportional to the dosage of statin therapy [114]. The clinical relevance of this association needs further investigation, especially in view of the fact that low testosterone has been indicated as a potential cardiovascular metabolic risk factor [115]. Epidemiologic data have demonstrated that low testosterone serum concentrations increase the future risk of developing type 2 diabetes mellitus [116]. Since low testosterone decreases lipolysis and increases fat accumulation in visceral adipose tissue, it is reasonable to assume that low testosterone causes deterioration of glycemic control at least in part because of its negative effects on visceral adiposity [115,116].

On the other hand, the effects of statins on estrogens do not appear to be as negative as for testosterone. In a study in women near or at menopause, endogenous estrogens were not significantly affected by pravastatin treatment [117]. Additionally, long-term administration of statins had no effect on serum estrogen and androgen levels in postmenopausal women receiving and not receiving oral estrogen replacement therapy [118].

Given the frequent concordance of metabolic diseases including diabetes, obesity, and metabolic syndrome with cardiovascular diseases associated with hyperlipidemia, it is important to understand the potential metabolic risks and benefits of therapies with distinct statins. Certainly, at present, clinical practice in patients with moderate or high cardiovascular risk or existing cardiovascular disease should not change. Nevertheless, considering the widespread adoption of statin therapy both in primary and secondary prevention in the general population, the clinician should be aware of these potential detrimental effects: further studies aimed at dissecting out the different metabolic effects of single statins would be very warmly welcome.

Specific metabolic drugs

Trimetazidine

Trimetazidine is a piperazine-derivate drug that has been reported to exert several beneficial effects in cardiac patients without affecting myocardial oxygen consumption and blood supply. It is a drug with a primary metabolic mechanism of action. The main

mechanism of action of trimetazidine is related to inhibition of oxidative phosphorylation by shifting energy production from fatty acid to glucose oxidation [119]. This beneficial metabolic adaptation is predominantly caused by a selective block of long chain 3-Ketoacyl coenzyme A Thiolase (3-KAT) activity, the last enzyme involved in beta-oxidation [119]. This agent has been shown to preserve phophocreatine and ATP intracellular levels in the failing heart [120] and to exert significant beneficial effects in patients with ischemic and non-ischemic left ventricular dysfunction [121]. These beneficial effects of the molecule have been incidentally observed to be mainly operative in patients who, apart from ischemic cardiomyopathy, are also diabetic [122] The mechanism of action is related to the property of trimetazidine to facilitate myocardial utilization of glucose instead of FFA which, in the context of malfunctioning myocardial cells, appears to be deleterious. Its inclusion in guidelines dealing with heart failure has been advocated [123].

It has also been observed that trimetazidine can reduce endothelin release in cardiac patients [124]. Trimetazidine-induced reduction of intracellular acidosis in ischemic myocardium [125] could not only influence myocardial but also endothelial membranes [126]. By decreasing endothelial damage, trimetazidine can inhibit ET-1 release that, keeping in mind the close relation between endothelium and insulin sensitivity, will increase insulin sensitivity. In fact, it has been shown that trimetazidine can also improve overall glucose metabolism, indicating an attractive ancillary pharmacological property of this class of drugs [127]. The known insulin resistant state in most cardiac patients is certainly aggravated in those patients with overt diabetes. This is particularly relevant in patients with both diabetes and left ventricular dysfunction. In this context, the availability of glucose and the ability of cardiomyocytes and skeletal muscle to metabolize glucose are grossly reduced. Indeed, since a major factor in the development and progression of heart failure is already a reduced availability of ATP, glucose metabolism alterations could further impair the efficiency of cardiomyocytes to produce energy. By inhibiting fatty acid oxidation, trimetazidine stimulates total glucose utilization, including both glycolysis and glucose oxidation. The effects of trimetazidine on glucose metabolism could therefore: (a) improve cardiac efficiency and (b) improve peripheral glucose extraction and utilization [127,128].

Ranolazine

Similarly to trimetazidine, ranolazine is a piperazine-derivate drug registered in Europe, Asia and USA for the treatment of chronic stable angina. Ranolazine exerts its anti-anginal effect mainly through the modulation of the late sodium current, thereby reducing the accumulation of intracellular Ca^{2+} [129]. Ranolazine is able to modulate other intracellular ionic currents thus also potentially exerting an anti-arrhythmic effect. For the same reason, however, the drug also has a pro-arrhythmic activity; in fact one of the most dangerous side effects associated with the administration of ranolazine is the QT interval elongation. For this reason, strict ECG monitoring is indicated in patients receiving ranolazine.

Ranolazine also results in a clear enhancement of glucose oxidation in rat hearts perfused under a variety of conditions, including ischemia and reperfusion [130]. These actions of ranolazine occur at the same concentration of ranolazine that inhibits late Na^{+}-current activity. This effect of ranolazine may account, at least in part, for its anti-ischemic efficacy in the absence of hemodynamic effects. The MERLIN-TIMI 36 trial demonstrated the efficacy of ranolazine in reducing one year mortality in patients with acute coronary syndrome and subsequent heart failure [131]. Further analysis of the Merlin-TIMI 36 data has also shown that ranolazine improves glycemic control in patients with acute coronary syndrome and no ST elevation [132]. Additionally, ranolazine significantly improves glycaemic control in diabetic patients [133] confirming that, apart from their primary cardiac action, this class of drugs also has important ancillary effect on glucose metabolism. Future studies will clarify the potential role of ranolazine as a metabolic modulator in cardiac and diabetic patients.

L-Carnitine and mildronate

L-carnitine is an essential cofactor of fatty acid metabolism, shuttling the end-products of peroxisomal fatty acid oxidation into the mitochondria and modulating the intra-mitochondrial acyl-coenzyme A/coenzyme A ratio. Several human and animal studies support a modest benefit in left ventricular energetics and function with L-carnitine administration [134]. Administration of the related propionyl-L-carnitine to injured rat myocardium results in improved functional recovery and glucose use, supporting the theory that L-carnitine's beneficial effects are due to its ability to increase glucose oxidation despite elevated FFA serum concentrations [134]. Nevertheless, its therapeutic value in ischemic heart disease and heart failure has never been consolidated. In fact, it is not clear whether the effects of different carnitine intracellular levels may significantly differ between disease conditions and health status. More recent studies indicate that carnitine availability per se is a key regulator of muscle fuel selection [135]. A 20% increase in muscle carnitine content in healthy volunteers modulated changes in whole-body energy expenditure and muscle fuel metabolism, consistent with a carnitine-mediated increase in muscle fatty acid oxidation as a consequence of increased muscle long-chain acyl-group translocation via CPT1 [136]. Conversely, it has also been proposed that the decline in muscle free carnitine availability that occurs in parallel with increasing exercise intensity [as a result of its acetylation by increased pyruvate dehydrogenase complex (PDC) flux] will ultimately limit CPT1 flux and thereby muscle fatty acids oxidation [137].

Additionally, a potential role of carnitine in atherosclerotic lesion development has been suggested. In fact, it has been shown that the hepatic production of trimethylamine-N-oxide (TMAO) from gut microbiota-derived trimethylamine (TMA) may enhance cardiovascular risk via promoting atherosclerotic lesion development. Since one source of TMA production via the gut microbiota appears to originate from L-carnitine, it has been postulated that the administration of this dietary source may be a critical factor promoting cardiovascular risk [138]. This is in contrast with the above mentioned beneficial properties for L-carnitine consumption against metabolic diseases including skeletal muscle insulin resistance and ischemic heart disease. Furthermore, fish are a significant source of TMAO, but dietary fish consumption and fish oil supplementation may exhibit positive effects on cardiovascular health. These objective discrepancies regarding L-carnitine supplementation and its possible negative effects on cardiovascular risk through potential increases in TMAO production, as well as its positive effects on metabolic health via increasing glucose metabolism in the muscle and heart, warrant further studies [139].

The issue about the potential positive/negative effects of L-carnitine supplementation becomes even more complicated when another story is introduced: meldonium (Mildronate). This is an anti-ischemic drug, originally developed in the 1970s as a growth-promoting agent for animals. Meldonium (3-(2,2,2-trimethylhydrazinium)-propionate), a γ-butyrobetaine (carnitine precursor) analogue, impairs liver carnitine biogenesis, accelerates

urinary free carnitine excretion, reduces muscle carnitine transport in vitro and reduces muscle carnitine availability and whole-body palmitate oxidation in vivo [140]. Since L-carnitine is involved in the metabolism of fatty acids, the decline in its serum concentrations stimulates glucose metabolism and decreases concentrations of L-carnitine related metabolites, such as long-chain acylcarnitines and trimethylamine-N-oxide. Meldonium has been shown to have some beneficial effects in cardiovascular, neurological and metabolic diseases due to its anti-ischemic and cardioprotective properties, which are ascribed mainly to its inhibition of fatty acid ß-oxidation and its activation of glycolysis. However, excessive reduction of muscle L-carnitine serum concentrations with meldonium has the potential to excessively decrease fatty acid ß–oxidation, and actually "starve" the muscle of energy. Apart from mere medical applications, meldonium has been adopted with the purpose of increasing exercise performance and post-exercise recovery rate. Recent reports from the World Anti-Doping Agency (WADA) indicate an alarming prevalence in the use of meldonium among elite athletes. Therefore, in January 2016, meldonium was added to WADA's prohibited list after being monitored since 2015 [140]. Nevertheless, there is a lack of studies performed with highly trained athletes and published in peer-reviewed journals that prove that meldonium actually improves exercise performance.

Conclusions

Most routinely used cardiovascular drugs yield ancillary energy metabolic effects that can either be beneficial or detrimental. Metabolic effects may be peripheral and/or directly influencing cardiac metabolism. Cardiologists and physicians looking after cardiovascular patients should be aware of the ancillary effects of the main drugs used in the daily clinical practice. Some of these metabolic properties may represent a principal effect of single drugs. All these concepts should prompt us to monitor peripheral and cardiac metabolic levels and try to improve them. Evidence-based medicine takes into account the beneficial effects of drugs on hard end-points, obtained by clinical trials of relatively short duration and it cannot be excluded that over longer time periods these beneficial effects of drugs could be either eliminated or reinforced due to their ancillary energy metabolic effects. For these reasons, future trials employing these drugs should take into account the evaluation of specific action on metabolism in order to better define their adoption in cardiac patients with different metabolic risk profiles.

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