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Platelet Activating Factor in Heart Failure: Potential Role in Disease Progression and Novel Target for Therapy

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Abstract Heart failure (HF) is a complex syndrome with cardiac, renal, neurohormonal and sympathetic nervous system's manifestations, the pathogenesis of which among others is connected to inflammation. PAF has local and systemic effects pertaining to HF progression since it causes a negative inotropic effect, it induces arrhythmias, it induces apoptosis and it is involved in inflammation and atherosclerosis. In the present review the role of PAF in HF will be thoroughly presented along with the relevant data on PAF enzymes and the potential role of PAF metabolic circuit as a novel pharmacological target.

Keywords Platelet activating factor · Inflammation · PAF-acetylhydrolase · Lipoprotein-associated phospholipase A2 · Lyso-PAF acetyltransferase · CDP-choline: 1-alkyl-2-acetyl-sn-glycerol cholinephosphotransferase · Heart failure

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Introduction

Heart failure (HF) is a complex syndrome, in which cardiac, renal, neuro-hormonal and sympathetic nervous system's manifestations are present [1••]. Despite the development of state-of-the art pharmacological agents, the incidence of HF increases at alarming rates [2], implying that several aspects of its pathophysiology remain undertreated. Indeed, the activation of the inflammatory cascade orchestrated by leukocytes, platelets, endothelial cells, myocardium together with other sources consists a key player in HF, which may have been overlooked [3]. Inflammatory markers differentiate along with the severity and progression of the disease [3] and may be modulated by HF-targeted drugs [4].

Although the isolation of the primary etiology of HF is not always easy, the leading cause of HF is atherosclerosis manifested as coronary artery disease (alone or in combination with hypertension) [1••]. Other causes include familial or acquired cardiomyopathy (due to viral infection, alcohol, heavy metals, chemotherapy, selenium deficiency, amyloidosis, etc.), valvular heart disease, pericardial heart disease, endocardial heart disease and arrhythmia [1••]. Moreover, hemodynamic disturbances such as those observed in renal failure or post-operative fluid infusion as well as high-output states such as anemia and thyrotoxicosis can lead to heart failure [1••].

Platelet-activating factor (PAF), (1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine) [5], is a potent inflammatory phospholipid mediator implicated in atherosclerosis [6, 7] and several mechanisms of HF [6, 8]. For example, PAF causes a negative inotropic effect, it induces arrhythmias, it induces apoptosis and it is involved in leukocyte recruitment [6, 8]. Moreover, recent data suggest that PAF metabolic enzymes may participate in HF development [9, 10•]. With respect to PAF metabolism (Fig. 1), two biosynthetic

pathways are responsible for its biosynthesis, namely the remodeling and the de novo pathway [11]. In the remodeling pathway a cytoplasmic phospholipase A2 converts the ether analogs of phosphatidylcholine to lyso-PAF, which is then acetylated to PAF by the action of at least two isoforms of acetyl-CoA: lyso-PAF acetyltransferases (lyso-PAF ATs), namely LPCAT1 and LPCAT2 [12, 13]. Recent data support that production of PAF by the action of LPCAT2 is activated under inflammatory conditions while LPCAT1 is calcium independent and does not participate in inflammatory processes [13]. The de novo pathway is considered to be responsible for the constitutive production of PAF. A key reaction in this route is the final one, in which PAF is produced by 1-O-alkyl-2-acetyl-glycerol through the action of a specific dithiothreitol-insensitive CDP-choline: 1-alkyl-2-acetyl-sn-glycerol cholinephosphotransferase (PAF-CPT, EC 2.7.8.16) [14]. As far as PAF catabolism is concerned, a PAF-specific acetylhydrolase (PAF-AH, EC 3.1.1.47) removes the acetyl chain (or short acyl chain) from sn-2 position and converts PAF to lyso-PAF [15]. The plasma isoform of PAF-AH is known as lipoprotein-associated phospholipase A2 (Lp-PLA2) due to its attachment to lipoproteins and mainly LDL-particles [15].

In the present review, the local and systemic effects of PAF pertaining to HF will be presented, particularly focusing on PAF effects on myocardium, its hemodynamic actions and its implication in atherosclerosis. Moreover, the relevant data on PAF enzymes will be discussed and the role of PAF circuit as a novel pharmacological target will be examined.

PAF and Myocardium

Inflammation of myocardium and myocardial necrosis caused by prolonged ischemia and hypoxia can lead to HF despite the existing compensating remodeling mechanisms (e.g., ventricular remodeling and neurohormonal stimulation). Moreover, contractile dysfunction and myocardial electrical instability constitute a central feature of HF [1••].

Metabolism of PAF in Myocardium

The exact cellular source of PAF in myocardium remains unknown. Many cell types may be responsible for PAF production under physiological or pathological conditions, i.e., endothelial cells, platelets, monocytes and other cells types including myocardial cells [16]. Myocardial cells produce PAF in vitro and in vivo under appropriate stimuli [6]. For example, immunological agents in guinea pig heart [17], ischemia in baboon and rabbit heart [18, 19] and injury in rat myocytes [20] can lead to PAF production. Confirming its role as an autacoid, PAF in turn exerts direct effects on myocardium, which are presented below.

PAF and Heart Contraction

PAF can influence heart contractility as a result of its hemodynamic effects (see below) or by directly acting on cardiac cells. PAF has been found to reduce heart's contractility in several models, such as guinea pig [21], dog [22] and rabbit hearts [23]. PAF infusion in isolated perfused guinea pig heart induces changes in cardiac cell structure such as myocardium oedema, decrease of matrix density, rapture of mitochondria crest and decreases of mitochondrial enzyme activities [24]. By this way, PAF impairs the generation of ATP through oxidative metabolism in the myocardium. The aforementioned changes are absent if treatment of myocardial tissue with the PAF antagonist BN 52021 precedes [24]. Moreover, trace elements such as zinc may reduce PAF's negative inotropic effect in low doses (1.5 μM) propably through modulation of PAF-receptor interactions [25].

Moreover, cell cultures demonstrate a direct effect of PAF on calcium [26] and potassium channels [27], which participate in myocardial contraction. Other hypotheses support the implication of leukotrienes [22], phosphatidyl inositol and PKC [28] as mediators of PAF-induced impairement of myocardial contraction. Indeed, genetically modified rats which do not express phosphoinositide 3-kinase-γ (PI3K-γ) are "resistant" to the negative inotropic effects of PAF [29]. Moreover, PAF induces the production of atrial natriuretic peptide [30]. Several data also suggest that PAF's actions in myocardium may be indirectly exerted through the production of reactive oxygen species by the recruited neutrophils [31]. Indeed, PAF inhibitors lead to reduction in PMNs in models of ischemia in rabbits [32].

Electrophysiological Effects of PAF in Heart

PAF can lead to changes in electrocardiograph in rats [33], guinea pigs [34] and rabbits [35]. PAF induces alterations in the transmembrane potential, i.e., increased duration of the action potential, early afterdepolarizations, transient arrest of repolarization [36] and abnormal automacity [37].

Other studies suggest that PAF induces anomalies in Purkinje cells function [38] and mice ventricular cells [37]. PAF seems to activate its specific receptors in the ventricle and induces arrhythmias [35], which are reduced in the presence of its inhibitors such as BN 52021, WEB 2086 [39, 40], kadsurenone [35] and *Ginkgo biloba* extract [41]. PAF induced arrhythmias are believed to be connected to the closing of potassium channels [37]. An additional route through which PAF may exert the above actions is the production of eicosanoids, since thromboxane A2 inhibitors also reduce PAF effects [42].

Hemodynamic Effects of PAF

The first indication of PAF's hemodynamic effects coincide with the identification of a polar lipid with

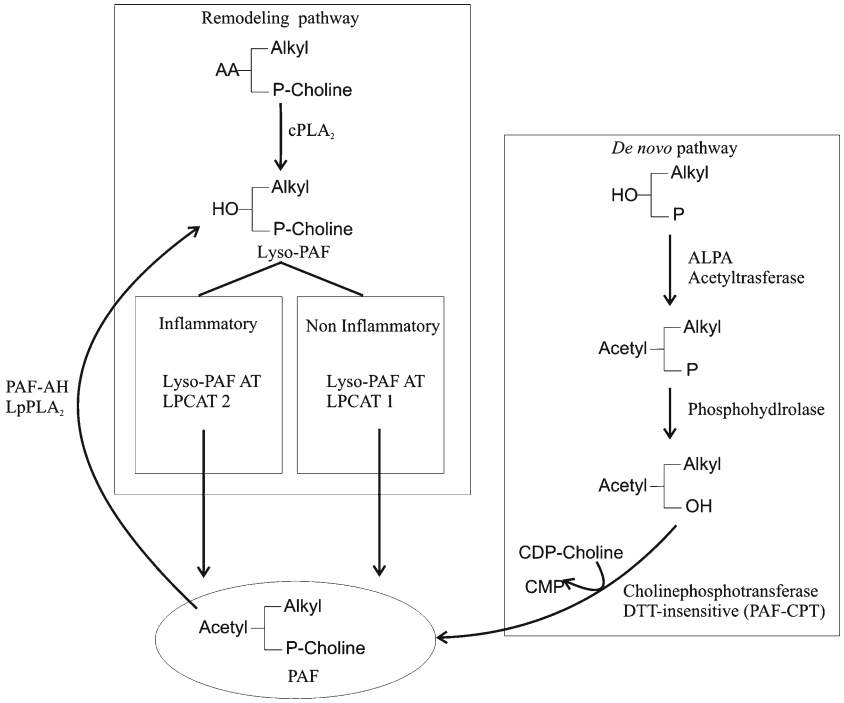

Fig. 1 The metabolic circuit of PAF

antihypertensive properties isolated from rat kidney (antihypertensive polar renomedullary lipid, APRL), which has proven to be PAF [43]. Intravenous or oral intake of PAF (or APRL) leads to a dose-dependent reduction in blood pressure in various animal species, which reaches a maximum within 30–60 seconds [6]. At concentrations 1–10 nmol/L PAF reduces coronary flow exerting a negative inotropic effect [44••]. In parallel hypertensive rats have increased Lp-PLA2 activity [45] while in a model of renal clip hypertension PAF acts as a mediator of blood pressure fall after unclipping [46].

The underlying mechanism of hypotensive effects of PAF has not been fully elucidated. Potential mechanisms through which the hypotensive effect of PAF is exerted are the following: (i) it reduces venous blood return, (ii) it produces a right ventricular overload as the result of an increase in pulmonary vascular resistance, (iii) it has a direct negative inotropic effect, and (iv) it affects heart's conductive system [6]. In line with the observations in animal species is the fact that increased right atrial pressure has been connected to increased PAF levels in patients undergoing coronary angioplasty [47]. PAF's hemodynamic effects may be exerted through PAF receptors, since selective PAF inhibitors such as *Ginkgo biloba* extract and BN 52021 extenuate the reduction of blood flow [48, 49].

Moreover, PAF may exert vasoconstriction effects by producing cyclo- and lipoxygenase metabolites, or by activating platelets and mononuclear cells. The vasoconstriction properties of PAF depend on its concentration range, the integrity of the endothelium and the animal model [44••].

PAF and Atherosclerosis

Atherosclerosis is a slow process orchestrated by oxidative stress, thrombosis and inflammation [50]. Chronic atherosclerotic burden in coronary and peripheral arteries leads to cardiovascular disease which is the most common cause of HF, as mentioned above [1••].

A crucial role of PAF in atherosclerosis has been proposed [7], since it constitutes an important mediator of inflammation [51] and is implicated in several stages of the disease. More particularly, it induces oxidative stress [52, 53], it participates in LDL oxidation [54] and it is produced during LDL oxidation upon Lp-PLA2 inactivation [55]. According to recent data oxidized LDL also interacts with PAF receptor in macrophages to increase oxidized LDL uptake [56] and stimulate chemokine release [57]. Moreover, PAF contributes to the adhesion of leukocytes [58] and their chemotactic entrance in endothelium, since it increases endothelial permeability [59].The PAF mediated activation of leukocytes also results in the secretion of chemokines and growth factors such as MCP-1 [60] and vascular endothelial growth factor (VEGF), respectively [61]. In parallel, PAF causes platelet aggregation [62] and stimulates the release of the stored cytokines and growth factors from platelets [63]. Moreover, it contributes to protease release from leukocytes,

such as elastase, which disrupts vessel's extracellular matrix [64] and may be a risk factor for plaque rupture.

It is thus obvious that PAF acts on various cells which participate in the atherosclerotic process such as platelets, endothelial cells, neutrophils and monocytes [7]. The secretion of PAF from some inflammatory cells, like monocytes and neutrophils can in turn result in the amplification of the inflammatory response [65]. The implication of PAF in atherosclerosis is also underlined by the observations that PAF inhibitors such as BN 52021 inhibit cholesterol deposition in arteries of animals fed an atherogenic diet [66]. A detailed review of PAF's contribution in atherosclerosis is provided by Demopoulos et al. [7].

PAF and Ischemia

Ischemia, which may be a result of the atherosclerotic process, can also exert its effects on myocardium through PAF. Several data suggest that PAF can play a role in cardiac myocyte death resulting from ischemia/ reperfusion injury by inducing apoptosis [8], which in turn can lead to cardiac dysfunction and HF [67]. Indeed, in concentrations of 0.2 to 20 μM PAF can cause apoptosis in cultured cardiac myocytes through a Ca2+-dependent mechanism. More particularly, PAF results in p38 MAPK phosphorylation, which in turn leads to cytochrome c/caspase-3 signaling activation and apoptosis [8].

However, in ischemia/ reperfusion states, PAF can also play a protective role as it is involved in ischemic preconditioning. Ischemic preconditioning refers to the fact that the myocardium adapts to brief periods of sublethal ischemia and is protected in case of a potential lethal ischemic injury [68]. Treatment with low concentrations of PAF, in the range of pM, before ischemia does not affect cardiac performance but exerts a protective effect, since it reduces infarct's extension and improves heart's recovery during reperfusion. Indeed, PAF activates kinases (such as PKC1, PKB/Akt, GSK-3b and ERK1/2), produces NO and affects calcium channels, all of which are implicated in the mechanisms of ischemic preconditioning [44••]. Supportive evidence of the PAF's protective role also involves the observation that post-ischemic performance is reduced in case of targeted deletion of the PAF receptor or if PAF receptor antagonists are used [69].

PAF's Metabolic Circuit and HF

Limited evidence exists for the role of PAF's metabolic enzymes in HF and cardiovascular diseases with the exception of Lp-PLA2. In a study of patients with newly diagnosed HF, we identified a possible relation of the remodeling and the de novo biosynthetic enzymes of PAF in leukocytes, since lyso-PAF-AT and PAF-CPT were correlated [9]. Moreover, both enzymes were related to inflammatory biomarkers [9], which are increased in HF [3]. More particularly, lyso-PAF-AT was positively related to CRP and IL-6 [9], which is in line with the fact that inflammatory stimuli are activators of this enzyme [70]. PAF-CPT was correlated to CRP and IL-6, suggesting that it may be implicated to pathophysiological processes involving inflammation [9], despite the proposed role for its contribution to basal PAF levels production [14]. Interestingly, PAF-CPT was also positively correlated with immunologic markers, i.e., CD40L and sCD14, while PAF-AH correlated to TNF-α [9]. Therefore, it seems that PAF's biosynthetic enzymes were depressed in HF patients and it was hypothesized that medical treatment affected PAF metabolic profile [10•]. Moreover, PAF levels seem to be low in patients with myocardial infarction at admission [71] and the expression of its receptor is upregulated [72].

Since PAF participates in atherogenesis, it can be assumed that its catabolic enzyme Lp-PLA2 may inhibit its atherogenic actions. Indeed, hyper-expression of Lp-PLA2 gene reduces atheromatous plaque [73]. However, Lp-PLA2 can also act as a pro-inflammatory molecule as it contributes to lyso-PC generation, which in turn leads to macrophage growth, non-esterified fatty acids and endothelial dysfunction [15]. Epidemiological studies have shown that Lp-PLA2 is a risk factor for cardiovascular disease. It is not certain, however, if Lp-PLA2 acts etiologically in cardiovascular disease or if it is increased as a response to increased PAF levels. It is noteworthy that several studies measure only the mass of the enzyme, which is not always indicative of its activity. Although the correlation coefficient between Lp-PLA2 mass and activity is 0.51 (0.47-0.56) [74••], almost 40 % of subjects in the highest quartile of the enzyme mass are in the lowest quartile of enzymatic activity [75]. The recently developed Lp-PLA2 inhibitors have shown some promising protective evidence [76–79] but their exact role remains to be determined [80]. As far as HF is concerned, Lp-PLA2 has been characterized as a prognostic biomarker for HF development [81, 82], is higher in HF patients than healthy controls [10•] and is associated with mortality in HF patients [83]. Moreover, it is higher in HF patients with preserved ejection fraction than in HF with reduced ejection fraction [84] and is not correlated with New York Heart Association (NYHA) status [85].

PAF as a Novel Target for HF Therapy

It is obvious from the aforementioned data that PAF is a crucial mediator of almost all pathophysiological mechanisms that lead to heart failure. Therefore, either its receptor or the enzymes of its metabolism seem to be attractive

targets for the treatment of HF. Moreover, several lines of evidence suggest that drugs designed to reduce inflammatory burden in HF, and mainly anti-TNF-a therapy have not always beneficial effects [86]. This observation underlines the necessity of drugs targeting to other molecules in order to further refine the therapy of HF patients.

Many HF drugs such as verapamil [87] and digoxin [88] reduce the PAF induced cardiac and circulatory alterations. In addition, the protective effects of the Mediterranean diet on HF patients [89] may be in part explained by the presence of PAF antagonists in foods. In fact, extracts of several traditional Mediterranean foods which are inversely related to atherosclerosis, such as olive oil, olive mill wastes, wine, fish, honey, milk and yogurt, as well as garlic and onion, contain PAF antagonists [90, 91]. Polar extract of olive oil, which acts as a PAF inhibitor, led to reduction of atheromatous plaque after 45 days in rabbits [92]. In patients with type 2 diabetes consumption of Mediterranean meals with high in vitro PAF inhibitory activity led to reduced platelet aggregation after PAF stimuli [93].

Recent data supports that newly diagnosed HF patients under drug treatment also have an affected profile of PAF biosynthetic enzymes and especially lyso-PAF-AT[10•]. Indeed, aldosterone antagonists, angiotensin-converting enzyme inhibitors, antiarrhythmic agents, statins and diuretics used in HF possess anti-inflammatory effects [94] although there are some studies not showing such effects [95]. Statins decrease Lp-PLA2 and PAF-CPT activities and have a neutral effect on lyso-PAF-AT activity in healthy volunteers [96]. Other possible interactions between PAF and cardiovascular drugs include nitrates and calcium channel blockers, which reduce PAF production in endothelial cells [97], and human umbilical vein endothelial cells [98], angiotensin-converting enzyme inhibitors which partly inhibit PAF effects and may lead to reduced PAF synthesis [99] and salicylates, which inhibit lyso-PAF-AT [100]. Thus, the existing medical treatment for HF may affect PAF biosynthetic enzymes. Whether the design of novel pharmaceutical products targeting on PAF enzymes would have beneficial effects on HF progression is not known.

It is therefore obvious that drugs commonly used for the treatment of HF affect PAF metabolism or its actions. Whether this is a direct effect of the drugs on PAF's enzymatic machinery/signal transduction pathway, or a secondary effect resulting from the anti-inflammatory properties of the HF treatment, is currently not known. However, in order to establish the pathogenetic role of PAF in HF, and therefore the necessity for its pharmacological modulation novel, well-designed, clinical trials should be conducted, wherein a putative reduction of PAF levels could be linked with an improvement of the HF clinical phenotype.

Another dilemma that arises from studies conducted so far is whether a candidate drug aiming on PAF metabolism/actions should be a PAF receptor antagonist or a modulator of PAF metabolism (inhibitor of its biosynthetic enzymes, activator of its degradation enzymes or an indirect modulator of its metabolism). With the current knowledge, the design of a molecule aiming on the PAFR/signal transduction axis is easier given that both PAF receptors and most of the components of their signal transduction pathways have already been characterized in the molecular level. On the other hand, such drugs may also inhibit PAF's physiological, homeostatic roles as well as its protective roles as in the case of preconditioning.

Alternatively, the designing of drugs aiming on the modulation of PAF metabolism may confer better specificity especially if they target enzymes of PAF metabolism that are upregulated under conditions that favor HF progression. As previously mentioned, the group of T. Shimizu characterized two lyso-PAF acetylating activities (LPCAT1 and 2) from which only one isoform was activated by inflammatory stimuli [12, 13]. The designing of specific inhibitors for this isoform would prevent the synthesis of PAF only under pathological conditions. However, the molecular details of the enzymatic pathways and the regulatory mechanisms of PAF metabolism are still obscure and only after their clarification the scientific community would be able to identify the best potential drug targets.

Finally, another aspect which deserves attention is the recent development of Lp-PLA2 inhibitor, namely darapladib. More particularly, darapladib reduces Lp-PLA2 activity, IL-6 and CRP in cardiovascular patients [76], prevents necrotic core expansion in atherosclerotic plaques [77] and decreases atherosclerotic plaque formation in ApoE-deficient [78] and LDL-R deficient mice [79]. However, the usefulness of this inhibitor in cardiovascular patients remains to be verified from ongoing clinical trials [80], while no evidence exists on the role of darapladib in HF patients.

Conclusions

In conclusion, PAF is a key player in HF progression since it causes a negative inotropic effect, it induces arrhythmias, it induces apoptosis and it is involved in inflammation and atherosclerosis. Recent data support that PAF metabolic enzymes may participate in atherosclerosis and HF development. However, the use of PAF and/ or its enzymes as pharmacological targets should be critically viewed and cautiously designed in the light of evidence that low PAF concentrations may have a cardioprotective role in ischemic preconditioning.

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- • Of importance
- •• Of major importance

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