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REVIEW ARTICLE

Cardiovascular complications in patients with autonomic failure

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Abstract Patients with autonomic failure are characterized by orthostatic hypotension, supine hypertension, high blood pressure variability, blunted heart rate variability, and often have a "non-dipping" or "reverse dipping" pattern on 24-h ambulatory blood pressure monitoring. These alterations may lead to cardiovascular and cerebrovascular changes, similar to the target organ damage found in hypertension. Often patients with autonomic failure are on treatment with anti-hypotensive drugs, which may worsen supine hypertension. The aim of this review is to summarize the evidence for cardiac, vascular, renal, and cerebrovascular damage in patients with autonomic failure.

Keywords Autonomic nervous system diseases · Orthostatic hypotension · Hypertension · Left ventricular hypertrophy · Arterial stiffness

Introduction

Autonomic failure (AF) is defined as the loss of function of the autonomic nervous system and includes, both primary and secondary forms. Primary neurodegenerative disorders, such as pure AF (PAF), multiple system atrophy (MSA), and Parkinson disease (PD), are characterized by the accumulation of the protein alpha-synuclein in the cytoplasm of central nervous system neurons, glia, and pre- and postganglionic peripheral autonomic neurons. Secondary forms of autonomic failure are primarily due to small-fiber neuropathies. The main secondary forms of autonomic neuropathy are those related to diabetes mellitus (DM), amyloidosis, immune-mediated neuropathies, and other systemic diseases [1].

Patients with AF often have high blood pressure (BP) variability [2]; on 24-h ambulatory BP monitoring (24-h ABPM), over 60 % of these patients show a "non-dipping" or "reverse dipping" pattern [2–4]. Supine hypertension is due to baroreflex dysfunction, nocturnal fluid retention, adrenergic hypersensitivity, and drug treatment for orthostatic hypotension [3, 5]. Orthostatic hypotension, supine hypertension, increased BP variability, and "non dipping" BP pattern may expose these patients to an increased risk of cardiovascular events, according to evidence in the literature on the general population and hypertensive patients [6–11].

We reviewed the evidence for cardiac, vascular, renal, and cerebrovascular damage in patients with AF.

Studies were selected from the PubMed database using the following keywords: autonomic failure, autonomic neuropathy, pure autonomic failure, multiple system atrophy, Parkinson disease AND left ventricular hypertrophy, arterial stiffness, peripheral artery disease, intima-media thickness, white matter hyperintensities, stroke, renal impairment, and renal failure. Retrospective, prospective, and cross-sectional studies were included. We selected articles in English language from 1984 to 2014. We also included conceptually related articles and expanded the bibliography by hand-searching references from selected articles. Main results are shown in Table 1. Similarities and differences in cardiovascular organ damage between essential hypertension and autonomic failure are summarized in Table 2.

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Table 1 Main studies regarding cardiovascular alterations in autonomic failure

Reference	Type of study	Number of patients	Type of AF	Main results
Heart				
Vagaonescu et al, 2000 [12]	Cross-sectional	14 AF, 14 EH, 12 C	Primary	Similar LVMi in AF and EH
Maule et al, 2006 [13]	Cross-sectional	25 AF, 20 EH	Primary and secondary	Similar LVMi in AF and EH
Gambardella et al, 1993 [14]	Cross-sectional	10 DM AF, 17 DM C	Secondary	Higher LVMi in AF
Irace et al, 1996 [16]	Cross-sectional	26 DM AF, 35 DM C	Secondary	Higher diastolic dysfunction in AF
Willenheimer et al, 1998 [20]	Cross-sectional	21 DM AF, 13 DM C	Secondary	Higher diastolic dysfunction in AF
Taskiran et al, 2004 [17]	Cross-sectional	10 DM AF, 10 DM C, 10 C	Secondary	Higher LVMi and diastolic dysfunction in AF
Karamitsos et al, 2008 [18]	Cross-sectional	18 DM AF, 26 DM C, 21 C	Secondary	Higher diastolic dysfunction in AF
Mogensen et al, 2012 [19]	Cross-sectional	26 DM AF, 30 DM C	Secondary	Higher diastolic dysfunction in AF
Pop-Busui et al, 2013 [15]	Cross-sectional	371 DM AF, 595 DM C	Secondary	Higher LVMi in AF
Arterial stiffness and blood vessels				
Huijben et al, 2012 [21]	Cross-sectional	10 AF, 14 C	Primary	PWV and AIx higher in AF
Meyer et al, 2004 [22]	Cross-sectional	33 DM AF, 22 DM C, 45 C	Secondary	Association between AF and increased PWV
Van Ittersum et al, 2004 [23]	Cross-sectional	76 DM AF/C*	Secondary	Association between AF and increased PWV
Prince et al, 2010 [24]	Cross-sectional	144 DM AF/C (19 symptomatic AF)	Secondary	Association between AF and increased AIx
Liatis et al, 2011 [25]	Cross-sectional	7 DM AF, 59 DM C	Secondary	Association between AF and increased PWV
Secrest et al, 2011 [26]	Cross-sectional	78 DM AF, 66 DM C	Secondary	Association between AF and increased AIx
Theilade et al, 2013 [27]	Cross-sectional	676 DM AF/C*, 51 C	Secondary	Association between AF and increased PWV
Nemes et al, 2010 [28]	Cross-sectional	25 C	None (Healthy controls)	Association between AF and increased PWV and AIx
Gottsäter et al, 2003 [29]	Cross-sectional	13 DM AF, 48 DM C	Secondary	Association between AF and carotid atherosclerosis
Gottsäter et al, 2006 [32]	Prospective	13 DM AF, 48 DM C	Secondary	Low HRV related to progression of atherosclerosis
Sinha et al, 2012 [30]	Cross-sectional	36 DM AF, 48 DM C	Secondary	Association between AF and increased IMT
Jung et al, 2013 [31]	Cross-sectional	40 DM AF, 91 DM C	Secondary	Association between AF and carotid atherosclerosis
Canani et al, 2013 [33]	Cross-sectional	67 DM AF/C*	Secondary	Association between low HRV and peripheral artery disease
Kidney				
Garland et al, 2009 [34]	Retrospective	64 AF, 75 C	Primary	Increased creatinine and decreased eGFR in AF
Torffvit et al, 1997 [35]	Cross-sectional	37 DM AF/C*, 33 C	Secondary	Increased degree of diabetic nephropaty in AF

Table 1 continued

Reference	Type of study	Number of patients	Type of AF	Main results
Bilal et al, 2008 [38]	Cross-sectional	53 DM AF	Secondary	Increased degree of diabetic nephropathy in AF
Kim et al, 2009 [37]	Retrospective	25 DM AF, 131 DM C	Secondary	AF predictor of deterioration in renal function
Pavy-le-Traon et al, 2010 [36]	Cross-sectional	684 DM AF/C (12.3% AF)	Secondary	Correlation between nephropathy and AF
Brain				
Lim et al, 2009 [39]	Cross-sectional	63 AF, 63 C	Primary	Increased WMH in AF
Tha et al, 2010 [41]	Cross-sectional	16 AF, 16 C	Primary	Increased WMH in AF
Umoto et al, 2012 [40]	Cross-sectional	22 AF, 22 PD AF/C*, 22 C	Primary	Increased WMH in AF
Oh et al, 2013 [67]	Cross-sectional	129 PD AF/C*	Primary	WMH in nocturnal hypertension
Struhal et al, 2013 [43]	Retrospective	50 AF	Primary	WMH and strokes in supine hypertension
Toyry et al, 1996 [44]	Prospective	133 DM AF/C*	Secondary	AF independent predictor of stroke
Cohen et al, 2003 [45]	Prospective	950 DM AF/C*	Secondary	AF independent predictor of stroke
Ko et al, 2008 [46]	Prospective	1458 DM AF/C (55.7% AF)	Secondary	AF independent predictor of stroke

AF autonomic failure, *C* controls, *PD* parkinson disease, *EH* essential hypertension, *DM* diabetes mellitus, *LVMi* left ventricular mass indexed to BSA, *WMH* white matter hyperintensities, *eGFR* estimated glomerular filtration rate, *IMT* intima-media thickness, *HRV* heart rate variability, *PWV* pulse wave velocity, *AIx* augmentation index

*Overall prevalence of AF not reported

Table 2 Organ damage described in essential hypertension and in autonomic failure

Organ damage	Hypertension	Autonomic failure	
		Primary forms	Secondary forms
Left ventricular hypertrophy	Present	Present	Present
Increased carotid femoral PWV	Present	Present	Present
Increased intima-media thickness	Present	Not assessed	Present
Peripheral artery disease	Present	Not assessed	Not assessed
Reduction in eGFR	Present	Present	Present
Microalbuminuria and proteinuria	Present	Not assessed	Present
Retinopathy	Present	Not assessed	Not assessed
White matter lesions and brain infarctions	Present	Present	Present

Heart

Several studies described cardiac damage in small groups of patients with primary forms of AF [12, 13]. Cardiac morphology and function were evaluated by transthoracic echocardiography and compared to patients with essential hypertension. Left ventricular mass was similar in subjects with AF and essential hypertension, but higher than in normotensive subjects. No differences were found between patients with MSA and those with PAF; patients affected by PD were not included in these studies. Vagaonescu et al. [12] found a weak relationship between left ventricular mass and mean 24-h BP values in a group of 14 patients with AF. Maule et al. [13] found higher BP standard deviations (marker of BP variability) in patients with left ventricular hypertrophy compared with those with normal left ventricular mass. A history of hypertension anteceding AF and treatment for OH does not seem to be related to the development of left ventricular hypertrophy [13].

In secondary forms of AF, such as diabetes mellitus (DM), heart damage has been evaluated after exclusion of patients with overt cardiovascular disease. In these patients, AF is related to an increased left ventricular mass evaluated by echocardiography [14] and cardiac magnetic resonance [15], independently of age, sex, 24-h ABPM values, and other clinical characteristics. Moreover, in these patients, diastolic function is also impaired [16]. These changes are related to increased sympathetic tone, increased BP variability,

decreased heart rate variability, and impaired myocardial blood flow regulation [17–19]. Parasympathetic impairment seems to represent one of the main determinants of diastolic dysfunction [20].

Arterial stiffness and blood vessels

To our knowledge, only one study evaluated arterial stiffness and central hemodynamics in patients with primary AF [21]. The study aimed to evaluate determinants of Pulse Wave Velocity (PWV), an index of arterial stiffness, and Augmentation Index (AIx), an index of central hemodynamics, using AF as a model of peripheral denervation. Ten patients affected by severe primary AF and a group of healthy controls were evaluated in supine and head-up tilt positions. Compared to controls, in AF patients, it was observed that carotid-femoral PWV, AIx, brachial and central BP values, and aortic and brachial pulse pressures were higher in the supine position. During head-up tilt, both carotid–femoral PWV and AIx decreased in AF, and the change was correlated to the drop in BP.

Many studies evaluated arterial stiffness in secondary forms of AF. In DM, arterial stiffness is inversely related to autonomic function [22–26]. Parasympathetic dysfunction (expressed as blunted heart rate variability) is strongly related to increased arterial stiffness and alterations of central hemodynamics [25, 27].

The relationship between cardiovascular autonomic function, arterial stiffness, and central hemodynamics was also studied in healthy volunteers. Heart rate response to deep breathing, Valsalva ratio, and the overall AF score correlated with PWV and AIx, while cardiovascular sympathetic tests did not correlate with aortic stiffness parameters [28].

In DM, the presence of autonomic neuropathy has been related to an increased intima-media thickness and to a higher burden of atherosclerotic lesions in the carotid arteries, but the actual causality relationship between these two factors is unknown [29–31]. Some authors argued that a reduction in heart rate variability, which may express an early autonomic dysfunction, could be related to a faster progression of atherosclerotic damage in patients with DM [32]. However, other studies did not find a relationship between atherosclerotic disease, defined by intima-media thickness, and the existence of AF [22].

Evidence is lacking regarding the exact relationship between AF and peripheral artery disease—but a lower heart rate variability has been described in patients with Type 2 DM and peripheral artery disease [33].

Kidney

Supine hypertension seems to have a preponderant role in causing renal functional impairment in primary AF. Garland et al. [34] retrospectively evaluated hemodynamic and laboratory data of 64 patients affected by PAF. Serum creatinine and urinary albumin were higher in PAF, while estimated glomerular filtration rate (eGFR) was lower in PAF than controls. Patients with PAF and supine hypertension had a higher serum creatinine level and a lower eGFR than those without supine hypertension.

In Type 1 DM, autonomic neuropathy is related to diabetic nephropathy [35, 36]. In Type 2 DM, patients with moderate to severe AF had a higher decline in eGFR during a mean follow-up of 9 years compared to those with normal autonomic function or early autonomic dysfunction at the time of diagnosis [37], as well as an increased prevalence of diabetic neuropathy [38]. In autonomic function tests, heart-rate response to deep breathing was independently associated with reduction in eGFR [37].

Brain

Cerebrovascular damage, represented by lacunar infarct, territorial infarct, and white matter hyperintensities (WMH), has been extensively studied in primary AF.

Patients with MSA have a higher degree of WMH compared to controls with similar age and cardiovascular risk factors [39–41]. BP in the supine position and the presence of orthostatic BP drop seem to be the most important determinants of cerebrovascular damage in AF. These factors, along with age, are independently related to the amount of WMH in MSA [39–41]. In PD, the presence and the extent of supine and nocturnal hypertension are strongly related to cerebrovascular damage [42]. In a recent retrospective study in PAF [43], 70 % of the patients had pathologic cerebral findings (WMH, lacunar strokes, hemispheric strokes, and microbleeds), but the prevalence of WMH seems to be lower in PAF than in the general population. Age and supine systolic BP were significantly higher in patients with pathologic findings. However, mean BP (as measured during the daytime, nighttime, and over a 24 h period), "non-dipper" status, and plasma catecholamine levels did not differ in patients with cerebrovascular lesions when compared to those without cerebrovascular lesions.

In secondary AF, diabetic autonomic dysfunction is an independent predictor of stroke in Type 2 DM [44–46]. The relationship between WMH and autonomic dysfunction has not been studied in secondary AF.

Other forms of organ damage

Hypertensive retinopathy is a relevant expression of hypertensive organ damage [47]. It has not been evaluated in primary forms of AF so far. In secondary forms of AF, namely diabetes mellitus, retinopathy is secondary to microangiopathy and the contribution of autonomic damage to the development of retinopathy is difficult to discern.

Pathogenesis of cardiovascular damage in AF

Cardiovascular complications in AF might share some pathophysiological aspects with target organ damage in essential hypertension.

AF patients are characterized by a very marked BP variability. In essential hypertension, target organ damage is correlated with BP variability, independent of baseline BP values [11, 48]. In AF, long-term BP variability indexes were found to be significantly higher in patients with left ventricular hypertrophy compared with those with normal left ventricular mass [13].

In PAF and in other forms of primary AF, the relationship between BP variability and impaired renal function has yet to be studied [34]. Long-term BP variability does not seem to play a role in cerebrovascular damage in AF [42].

In essential hypertension, the non-dipping BP pattern is related to a higher degree of cardiac alterations than a dipping pattern [49]. In AF, supine hypertension and reverse BP pattern may also play a role in cardiac [12], renal [34], and cerebrovascular damage [40, 43].

Orthostatic hypotension, the hallmark of AF, is associated with left ventricular hypertrophy in hypertensive patients [50], and is a risk factor for incident chronic kidney disease, heart failure, stroke, atrial fibrillation, coronary events, and overall mortality in the general population [6–9, 50, 51]. However, the relationship between orthostatic BP drop and the presence of cardiovascular damage is not well defined in AF, except for the white matter lesions [40, 41].

A blunted heart rate variability, typical of AF, is related to increased renal and vascular damage in hypertensive patients [52] and may contribute to the pathogenesis of vascular stiffness in AF [25, 27].

Except for rare, congenital forms, AF is more common in middle-aged and elderly patients; nonetheless, ageing does not seem to be significantly related to an increased prevalence of cardiovascular damage in AF in most studies.

Increased arterial stiffness is related to higher BP variability [53], impaired heart rate variability [27], and orthostatic hypotension [54, 55] in hypertensive patients. The interactions between arterial stiffness, hemodynamics, and subtypes of AF have yet to be studied.

Other mechanisms, unique to AF, might contribute to cardiovascular alterations in these patients.

In AF, anti-hypotensive drugs are widely employed. Fludrocortisone is a synthetic mineral corticoid analogue that increases sodium reabsorption and extracellular volume [56]. It may also induce fibrosis, with a mechanism of action similar to that of aldosterone. Few studies have evaluated the influence of this therapy on cardiovascular alterations in AF. In patients with and without left ventricular hypertrophy, the number of AF patients treated with fludrocortisone was similar in both groups [13]. The influence of anti-hypotensive therapy on cardiovascular alterations in AF has yet to be addressed in specifically designed studies.

The cardiovascular alterations in MSA may in part be explained by residual adrenergic sympathetic tone on super-sensitized receptors, in coordination with baroreflex failure [5]. Patients with PAF have very low levels of plasma norepinephrine and plasma renin activity, however, plasma aldosterone levels are normal [57], and angiotensin II is significantly higher than in controls [58]. Angiotensin II might also play a role in cardiovascular damage in AF.

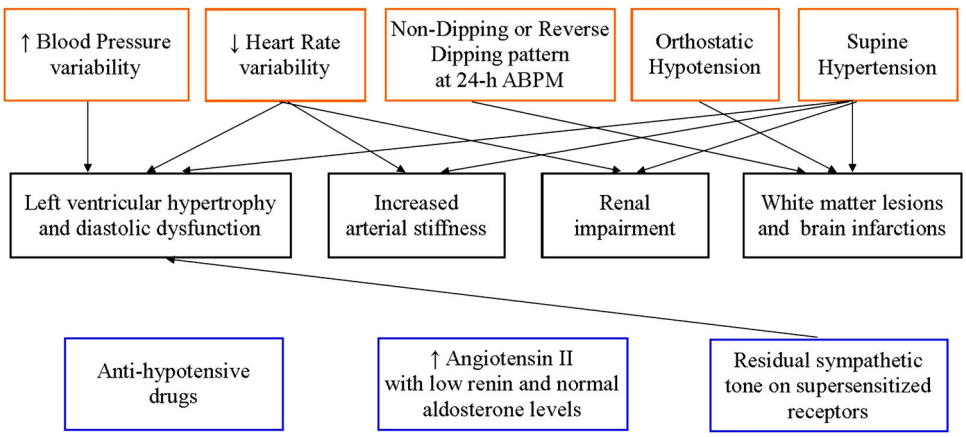

Fig. 1 Pathophysiological aspects and potential mechanisms determining cardiovascular alterations in AF. *Black boxes*: target organ damage occurring in essential hypertension and AF. *Red boxes*: potential mechanisms of target organ damage in AF that are similar to essential hypertension. *Blue boxes*: potential mechanisms of target organ damage unique to AF. *Black arrows*: evidence discussed in the text

Pathophysiological aspects and potential mechanisms determining cardiovascular alterations in AF are summarized in Fig. 1.

Secondary forms of AF are characterized by additional and different mechanisms of organ damage. In diabetes mellitus, microvascular and macrovascular alterations elicit cardiovascular complications; in amyloidosis, the deposit of amyloid in the heart determines the typical restrictive cardiomyopathy. In primary forms of AF, pathophysiological mechanisms are primarily related to alterations of blood pressure and cardiovascular regulation, typical of autonomic dysregulation.

Prognostic implications of cardiovascular damage in primary AF

The presence of AF is related to an increased mortality in diabetes [59], and orthostatic hypotension is related to an increased risk of all-cause mortality in the general population [10]. Hypertensive organ damage is related to an increased cardiovascular risk and therefore to a worse prognosis in essential hypertension [47]. The prognostic role of cardiovascular damage in primary AF is not known.

MSA patients have a poor prognosis overall [60]. Major causes of death in MSA include infectious diseases and sudden death [61–63]. Due to the rapid course of the disease, early detection of cardiovascular damage may be less relevant in these patients.

Causes of death in PAF patients are less well-known, although the prognosis seems good [63, 64]. These patients may be exposed to an increased risk of cardiovascular complications and mortality due to orthostatic hypotension and high BP variability [6–11].

PD has a better prognosis than MSA. Infectious diseases such as pneumonia, are a common cause of death in patients with PD. Cardiovascular mortality and sudden death have also been reported [65, 66]. Early detection of AF in PD is important so that patients may begin treatment for orthostatic hypotension, which is a common side-effect of anti-parkinsonian drugs. Specific treatment of orthostatic hypotension will address symptoms associated with low blood pressure, reduce the risk of falls, and improve quality of life for these patients.

In conclusion, for clinical practice, the detection of supine hypertension is crucial and allows clinicians to choose the most appropriate drug therapies—indeed, 24 h ABPM is a valuable diagnostic tool that can be used to identify this in patients with AF. Orthostatic hypotension is usually treated with short-acting drugs such as midodrine, and careful adjustments need to be made to the time of administration in patients who have severe cases of nocturnal hypertension.

Prospective studies evaluating the impact of cardiovascular alterations on the prognosis of AF are still lacking, as are studies evaluating the impact of the treatment of supine hypertension on the prognosis. It is not known whether the early treatment of supine hypertension may prevent the onset of cardiovascular damage in AF.

The study of cardiovascular alterations in AF patients allows for better understanding of the natural history of AF and the pathophysiological mechanisms of hypertension-induced cardiovascular damage.

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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