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Neurocardiovascular instability may modulate end-organ damage: A review of this hypothesis investigating the eye and manifestations of NCVI

Bláithín Ní Bhuachalla [a,*], Christine A. McGarrigle [b], Rose Anne Kenny [a,b,1]

[a] Discipline of Medical Gerontology, School of Medicine, Trinity College Dublin, Old Stone Building, Trinity Centre for Health Sciences, St James's Hospital, James's Street, Dublin 8, Ireland
[b] The Irish Longitudinal Study on Ageing (TILDA), Lincoln Gate, Trinity College Dublin, College Green, Dublin 2, Ireland

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ABSTRACT

Neurocardiovascular instability (NCVI) represents age-related changes in blood pressure and heart rate behaviour. It has been associated with increased leukoaraiosis in the brain and also conditions which are likely to be are related to cerebral end-organ damage, such as stroke and falls. The eye is a 'window' into the brain and cardiovascular (CV) system, changes in retinal microvasculature being independently predictive of cardiovascular events. The eye is highly vascular, having two circulatory systems and as such the ideal target end-organ to investigate NCVI and early end-organ damage. The retinal and choroidal circulations of the eye would be vulnerable to NCVI if ocular vasoregulation becomes impaired with age, particularly given the high metabolic activity of the retina. The choroid is predominantly extrinsically regulated by the autonomic nervous system. In patients with NCVI, autonomic dysfunction is more common and thus impairment of the tightly regulated ocular microcirculation may indeed be compromised. We review the evidence for the hypothesis that NCVI may modulate end-organ cardiovascular pathology and that the eye is the ideal target organ to monitor this.

Introduction

Cardiovascular diseases are the leading cause of morbidity and mortality globally [1]. In the context of the exponentially ageing population [2], identifying those vulnerable to accelerated cardiovascular risk has never been more important. Studying end-organ cardiovascular pathology will provide insight into this. The eye is ideal for this purpose, particularly as the retina has the highest oxygen consumption per volume in the body [3] and requires tightly autoregulated ocular blood flow. Neurocardiovascular instability (NCVI), defined as age-related changes in blood pressure (BP) and heart-rate behaviour [4] manifests as exaggerated blood pressure variability, hypotension, hypertension, carotid sinus hypersensitivity, cardiac arrhythmias and autonomic dysfunction. Unstable oxygen supply, a consequence of unstable blood flow, such as that caused by NCVI, induces oxidative stress [5]. Risk factors for vascular aging include hypertension and diabetes and these are also risk factors for NCVI, particularly orthostatic hypotension (OH) [6]. Oxidative stress, inflammation and vascular ageing are interconnected and central to poor cardiovascular health [7]. We review the age-related associations between the eye, a target cardiovascular end-organ, and NCVI.

Neurocardiovascular instability

In a healthy individual, orthostatic change results in up to a 1 l of blood pooling in the lower extremities. This venous pooling causes a transient reduction in left ventricular (LV) filling and consequentially cardiac output. This triggers the arterial baroreflex which increases sympathetic outflow with resultant increase in total peripheral resistance and heart rate (HR) [8]. In this way the orthostatic drop in BP is compensated for and BP recovers to baseline. Changes in cardiovascular (CV) and autonomic nervous system (ANS) physiology with age, cause altered BP and HR responses to stimuli such as orthostasis and manifest as NCVI.

While the underlying mechanisms of NCVI are not fully understood, it predominantly manifests as hypotension and bradyarrhythmia [9]. Factors contributing to age-related NCVI include altered neural and endothelial regulation of vasculature, blunted baroreflex sensitivity and changes in cerebral autoregulation. Humoral changes such as decline in plasma renin and aldosterone have the effect of reducing intravascular volume, which augments

* Corresponding author. Tel.: +353 87 6186945; fax: +353 1 896 2451.
E-mail address: nibhuacb@tcd.ie (B. Ní Bhuachalla).
[1] Tel.: +353 1 8964084.

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reduced LV filling and consequent drop in BP. Additionally polypharmacy and comorbidity, increasingly common with advancing age, exacerbate manifestations of NCVI e.g. beta blockers prevent adequate compensatory heart rate response to hypotension [9].

The most common clinical presentations of NCVI include carotid sinus syndrome, vasovagal syncope, post-prandial hypotension and OH. In this review we discuss OH and two other manifestations of NCVI, considered less often, orthostatic hypertension (OHTN) and blood pressure variability (BPV). These three conditions have been implicated in CV risk and resultant end-organ damage.

Orthostatic hypotension

Classical OH is defined by consensus statement as a sustained reduction in systolic blood pressure (SBP) of at least 20 mmHg and/or diastolic blood pressure (DBP) of 10 mmHg within 3 min of standing [10]. This definition is based on auscultatory and oscillometric measures [11]. The published prevalence of OH varies and ranges from 6% to 34% in home dwelling elderly individuals [8,12,13]. Newer methods of BP assessment using digital photoplethysmography enable beat-to-beat BP measurement. Furthermore research investigating the clinical significance, of SBP responses to orthostasis, using this newer method of measurement, demonstrate distinct age-related gradients i.e. median SBP recovery in men aged 50–59 years was within 20 s of standing, compared with a median recovery at 50 s after standing for men $\geqslant$80 years [14]. OH has pathological associations and this more subtle age-related variation in 'time to stabilisation' of orthostatic SBP is likely to have clinical significance also. Indeed a sustained BP drop at 40 s after standing is associated with increased odds of reporting falls on clinical history [15].

In a community based population study, OH was independently associated with poorer global cognitive function and memory in women $\geqslant$65 years [16]. Individuals with systolic hypertension (SH) (defined as BP > 140/90 mmHg) coupled with OH also had lower global and executive cognitive function [17]. Earlier studies have shown that the prevalence of OH and autonomic neuropathies is higher in patients with dementia [18], and that OH is three to five times more frequent in Alzheimer's dementia (AD) and vascular dementia compared to healthy age-matched controls [19] leading to speculation that unstable blood pressure and impaired cerebral autoregulation may play a role in pathogenesis of cognitive impairment and dementia [20,21].

Initial OH, which refers to a drop in SBP or DBP of >40/20 mmHg within 15 s after standing, together with symptoms of orthostatic intolerance, is associated with higher prevalence of falls and frailty cross-sectionally [22]. More recent data has shown that failure to stabilize SBP is also associated with falls and injuries both cross-sectionally and at two year follow up [14,15]. Furthermore, Tinetti's group have recently reported that more aggressive antihypertensive treatment in elders in the US is associated with higher rates of falls and fractures [23]. We have also recently reported an association between syncope and stroke events and related this to abnormal orthostatic BP behaviour in susceptible syncope patients [24]. However a meta-analysis, evaluating the evidence that OH is an independent CVS risk factor, included 28 prospective studies found however a paucity of prospective studies that investigated OH in relation to either stroke or falls and hence meta-analysis in relation to these was not possible. [25].

Adults with OH, particularly symptomatic OH, have a higher independent risk of developing new onset heart failure [26]. Overall OH is associated with higher CV risk [27], an increased risk of all-cause mortality [28] and indeed an overall mortality increased risk of 36% [25]. Therefore while evidence linking OH and specific clinical entities is varied and limited for some, there is more substantive evidence linking it with overall CV risk and mortality.

Orthostatic hypertension

Orthostatic hypertension has been defined by elevation in BP on standing, the absolute value of the increase differing in studies, ranging from 5 mmHg to 20 mmHg. Others have defined it as the development of hypertension on standing i.e. a change in SBP from <140 mmHg to $\geqslant$140 mmHg after standing [29]. Prevalence ranges from 9% to 16% depending on the definition used [30–33]. One population study defining an increase in SBP of >20 mmHg, 1 minute after standing, as OHTN, noted that a higher proportion of those with OHTN were of black ethnicity, with a higher mean seated SBP and had a greater risk of developing coronary heart disease after 8 years [34]. OHTN has been found to be more common in those who are diabetic [32] and is associated with worse neurobehavioral function and greater leukoaraiosis and silent infarction on MRI brain imaging [30,33]. Hence some have proposed that OTHN may be a stand-alone cardiovascular entity and risk factor [29] although to date, with only 20 cross-sectional studies in the literature, it has been less often considered compared to OH.

Blood pressure variability

Blood pressure variability (BPV) is defined according to different time periods: (a) very short intervals (beat-to-beat variability), (b) short intervals over 24 h, (c) diurnal variation over 24 h and longer time intervals, including (d) day-to-day variability and (e) visit-to-visit variability, typically over months to years [35]. Studies have investigated the clinical significance of diurnal BPV over the 24 hours, day to day BPV and visit-to-visit BPV [36]. Beat-to-beat BPV has not been widely studied but is often recorded with heart rate variability (HRV). Reduced HRV is significantly associated with lower cognitive performance at a population level in people aged $\geqslant$50 years [37] and has been observed in patients with hypertension and chronic kidney disease [38]. It is an independent predictor of mortality in survivors of myocardial infarction [39].

Each form of BPV, as above defined, are considered distinct clinical entities. Intuitively one can hypothesise that different types of BPV may share similar underlying mechanisms or patients presenting with different forms may have similarities in their cardiovascular risk profiles. This has been under investigation however and no definitive conclusions about the relationship between different types of BPV can as yet be made. However, if beat-to-beat BPV, for example, was a marker of other types of BPV, already established to increase CV risk, this would clinically be important, given ease of measurement of beat-to-beat BP with newer technologies.

Abnormal diurnal BPV on 24 hr ambulatory BP monitoring (ABPM) is established to increase risk of CV events, end-organ damage and CV mortality. Examples include morning hypertension and reverse dipping [36,40–42]. The within-individual standard deviation (SD) of visit-to-visit SBP has been reported as 10–20 mmHg [36] and hence anything greater can be considered increased visit to visit BPV. While the overall prognostic value of visit to visit variability is not established, it is an independent risk factor for stroke [43].

A recent study assessed the validity of short-term beat-to-beat BPV as a marker of ambulatory and day-to-day BPV in a cohort of 233 patients who had experienced either a transient ischaemic attack (TIA) or minor stroke within the prior 6 weeks [44]. Beat-to beat BPV was defined as the coefficient of variation (standard deviation/mean) of SBP at normal R-R intervals from 5 min of supine monitoring (after 20 min supine rest). The R-R interval refers to the time elapsing between two consecutive R waves on the electrocardiogram. Coefficient of variation was also used to

define day to day BPV and BPV on ABPM. Beat-to-beat BPV was associated with day-to-day BPV on all readings, at each time of day and within-day. No association was found with awake ambulatory BPV. In this study associations were also investigated between different physiological characteristics and each type of BPV. Similar associations were found for age, aortic pulse wave velocity, aortic pulse pressure and HRV for both beat-to-beat BPV and day-to-day BPV but not ambulatory BPV [44]. Given that these measures include indices of CV health, it does support the argument that there may indeed be common underlying mechanisms between some types of BPV. However the fact that no relationship was found for ambulatory BPV suggests relationships are likely to be complex. In addition this study investigated a very specific subgroup that had already experienced a CV end-organ event.

Wei et al. investigated whether there was an association between different types of BPV and markers of target end organ damage in 256 untreated Chinese subjects referred to a hypertension clinic [45]. The objective was to assess any evidence of correlation between left ventricular mass index (LVMI), the urinary albumin-to-creatinine ratio, and aortic pulse wave velocity (PWV) with 10-min beat-to-beat BPV, 24-h ambulatory BPV, and 7-day home BP recordings. Different correlates of BPV were used including, variability independent of the mean, difference between minimum and maximum BP and average real variability which is the average of the absolute differences between consecutive BP measurements. A key finding was that these 3 indices of 10-min BP variability were associated with increased LVMI independent of level of mean BP [45].

In conclusion, whether BP variability predicts CV risk better than mean BP is not yet clear. The relative few studies of BPV have been in select populations. Studies have used different definitions of BPV and are thus not comparable. In addition the phenomenon of orthostatic beat-to-beat BPV has not been studied at all to our knowledge. Given that other types of orthostatic BP behaviour have been associated with increased CV risk, we argue that orthostatic BPV merits investigation in its own right. Overall further research is needed before there is clarity.

Why should the eye be vulnerable to NCVI?

Watershed zones of the retinal and choroidal circulations

The inner two-thirds of the retina are supplied by the retinal circulation. The outer one-third, which contains the most metabolically active photoreceptors and the fovea, the point of sharpest central visual acuity, are supplied by the choroidal circulation [46,47]. Both circulations are derived from the ophthalmic artery, the first branch of the internal carotid artery. The retinal arteries branch and create a vertical watershed between both halves of the retina. There are no inter-arterial connections thus it is an end arterial system [48]. The choroidal circulation, supplied by the anterior and posterior ciliary arteries [49] also has clear watershed zones. These are subject to inter-individual variation [50] and their location has been implicated in ischaemic optic neuropathy (ION) [51], which in turn implicates hypotension in pathogenesis. The photoreceptors of the fovea are relatively distant from their blood supply in the choriocapillaris. Hence even small decreases in blood flow may have significant clinical implications, particularly in the context of watershed perfusion [52]. We hypothesise that the optic nerve and retina are more vulnerable to ischaemia in watershed zones with increasing age, due to NCVI which also increases with age (Fig. 1).

The blood–retinal barrier

The eye has a blood–retinal barrier (BRB) (inner and outer) which is similar in structure and function to the blood–brain barrier (BBB). Their function is to protect the neural milieu, including against oxidative stress. However there are differences between the blood–brain barrier and both the outer blood retinal barrier (retinal pigment epithelium i.e. comprised of epithelial cells in contrast to endothelial cells in the brain) and the inner blood retinal barrier (endothelial cells). These differences make the eye more vulnerable to oxidative stress and hence potentially could confer increased vulnerability of the eye to adverse outcomes from NCVI.

To date it has been animal studies, which have provided evidence of differences between BRB and BBB. It is beyond the scope of this review to discuss these in detail. However, these differences offer some explanation as to the greater pathological effect of diabetes on the retinal microcirculation (diabetic retinopathy) compared to the cerebral circulation, for example. In one study bovine brain and retinal endothelial cell cultures were incubated in glucose containing mediums for 5 days and then analysed. Junctional protein (ZO-1) levels limit endothelial cell permeability. In the brain derived cells, ZO-1 levels increased in response to glucose, but were unaffected in the retinal-derived cells [53]. In addition, the retinal endothelial cells demonstrated lower levels of ZO-1 and superoxide dismutase, as well as lower activity of the enzyme glutathione peroxidise. The latter two enzymes reduce metabolites of oxidative stress and prevent cellular damage [53].

Autoregulation of ocular circulation

Blood flow within the eye is dependent on multiple factors, including the perfusion pressure (mean arterial BP minus intraocular pressure) and the resistance to flow, determined by the vascular calibre in the arterioles and capillaries. Systemically vascular calibre changes as needed, through vascular autoregulation. This is endothelium dependent but controlled by a balance of myogenic, metabolic and humoral factors in addition to neural influences.

Because some vasoactive molecules are too large to pass through the blood–retinal barrier and hence have lesser access and less influence on the smooth muscle cells and pericytes of the retinal vessels, other mechanisms unique to the eye play a dominant role. ‘Neurovascular coupling’ refers to the link between the neural activity or metabolism of the retina and the vasomotor tone of the retinal vasculature. The release of nitric oxide (NO) and lactate by glial and neuronal cells are detected by the retinal endothelium. This triggers vasodilatation or vasoconstriction, hence altering the blood flow to meet the needs of the retinal tissue and maintain homeostasis. States of hypoxia and hypercapnia are important influencing factors also [48,54]. Similar to elsewhere in the arterial system the vasculature of the retina exhibits intrinsic myogenic tone, and perfusion pressure influences flow mediated dilation in retinal arterioles and capillaries, independent of metabolites or hormones [46]. Increased transmural pressure equally induces release of endothelial factors which stimulate vasoconstriction [48]. Uniquely, light-to-dark transition or a flicker stimulus influences retinal vascular tone [48].

Choroidal blood flow is regulated somewhat differently to retinal blood flow. Vessels are sensitive to vasoactive substances released by the endothelium. Given the highly permeable nature of the fenestrated choriocapillaris, large circulatory molecules such as hormones have an effect on vascular tone, for example, angiotensin II. There is less local or intrinsic regulation in choroidal blood flow due to less local pericytes in the microvasculature and lack of coupling to the activity of glial cells. Instead the choroidal vasculature is densely innervated by sympathetic and parasympathetic fibres from the ANS or extrinsic regulation. Changes in perfusion pressure do trigger autoregulation but it is not clear whether this is mediated by a myogenic or neuronal mechanism [55]. There is little literature regarding the influence

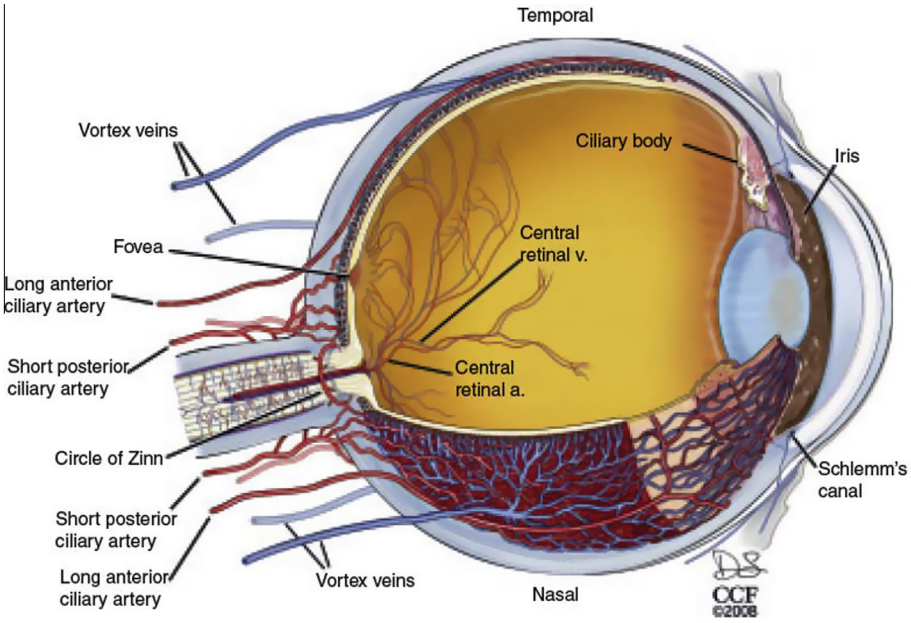

Fig. 1. Circulation of the eye.

of arterial blood gases on the choroidal circulation but animal studies suggest that pCO_2 but not PO_2, is an important dependent factor. Light stimulation is also thought to have little regulatory effect on blood flow but research is limited [46].

It is unknown whether age impairs ocular blood flow regulation analogous to the age-related systemic BP changes. It is possible that age-related changes in the ANS could exert an effect on regulation of the choroidal circulation. Animal studies have shown that there is an age-related impairment in choroidal blood flow regulation in pigeons when systemic BP was above and below the 'basal' range of BP [56]. Overperfusion of the retina occurred with above basal range BP and underperfusion at below basal range.

Although, little is known of the influence of age on autoregulation of retinal blood flow, it is likely that age-related arterial stiffness, vascular remodelling, atherosclerosis and endothelial dysfunction contribute to autoregulatory dysfunction. The appearance of the optic disc with increasing age is similar to that seen in glaucoma and as will be discussed, different forms of glaucoma have been associated with impaired regulation of systemic BP and autonomic dysfunction [57–59] i.e. manifestations of NCVI. Since NCVI is an age-related condition this underscores a potential age – related impairment in retinal circulation autoregulation.

Existing associations between eye pathologies and NCVI

Despite plausible biological hypotheses for an association between NCVI and age-related eye disorders, there is a paucity of studies in this area. Changes occur in the ageing visual system at the level of optics within the eye, the retina and choroid, the ocular circulation and cortically in terms of visual processing. All of these contribute to age-related impairment in visual function. Reduced visual function can be quantified by visual acuity (VA) and visual contrast sensitivity (CS) measures.

VA is a measure of the ability to detect progressively smaller, high contrast, black letters on white background, which is ideally suited to diagnosing refractive error rather than global visual function. CS is a measure of the limit of perception of a faded image. In many ocular diseases CS may become impaired early in the pathological process, while VA may not. Clinical measures of CS typically represent the sum effectiveness of the total visual pathway involving the optical eye media, the retina and the brain together. Hence impaired CS may represent pathology at any or multiple levels of this pathway.

In addition to a myriad of age-related physiological changes, specific age-related eye diseases also contribute to age-related visual impairment. The most prevalent eye diseases of age include refractive error (most commonly presbyopia), cataract, age-related macular degeneration (AMD), glaucoma, diabetic retinopathy and hypertensive retinopathy. Clearly the latter two conditions are established to be strongly linked to cardiovascular disease. However the pathophysiology of cataract, age-related macular degeneration and glaucoma have all been associated with cardiovascular risk and for all, there may be interplay with potential vascular aetiology [60–62].

Cataract is the leading cause of blindness worldwide [63]. There are different phenotypes of cataract, namely nuclear, cortical and posterior subcapsular lens opacities and the epidemiology of these is different. However established risk factors for cataract include: diabetes, chronic ultra-violet light exposure, medications (steroids), smoking and genetics [64]. Hence there is a clear association with cardiovascular risk. Animal studies offer evidence that oxidative stress plays a role in lens opacification but clinical trials of anti-oxidants have not been proven to be of benefit. However the methodology of these studies has been criticized [64] and this is an area of active research [65]. To our knowledge there are no studies investigating associations between cataract and NCVI specifically but it is interesting that oxidative stress has been implicated in pathogenesis given the link between the latter and NCVI. In addition, there is not a consensus but some large epidemiological studies have found an association between cataract and mortality. A study of the Salisbury Eye Evaluation Project reported that lens opacity status was an independent predictor of 2-year mortality, after adjustment for health status, frailty, and other confounders [66]. Analyses of cause specific mortality suggested a $\geqslant$2-fold risk associated with mixed nuclear opacity for cancer and similarly for cardiovascular causes, although the latter was not statistically significant.

Some studies report an association between glaucoma and components of NCVI. There is a consistent trend of autonomic dysfunction, increased BP variability, particularly nocturnal BP variation

Table 1
Glaucoma and orthostatic hypotension.

References	Participants (N)	Predictor variable	Outcome assessed	Main results
Park et al. [57]	Eyes with NTG[a] and more than 7 visual field tests during at least 5 years of follow up were analysed retrospectively (48)	HR[b] variability	Rates of change in mean thresholds of each designated visual field region	NTG[a] patients with lower HR[b] variability, which reflects autonomic dysfunction presented faster rate of central VF[c] progression than patients with higher HR[b] variability
Nesher et al. [59]	Patients with NTG[a] and episodic dizziness but no confirmed diagnosis of OH[d] (11)	24 h monitoring of BP[e] and HR[b]. The cardiac dDP[f] and sDP[g] at each reading were calculated by multiplying the HR[b] by the respective BP[e]	To identify if combined bradycardia-hypotension during 24 h APBM[h]	Abnormally low dDP[f] was recorded in all NTG[a] patients, lasting >1 h in the majority, which may represent CV[i] autonomic dysregulation, resulting in low ocular perfusion in certain NTG[a] patients
Yong et al. [83]	Participants who had had an episode of acute angle closure (symptomatic PACG[j]), those who had asymptomatic PACG[j], and age and sex-matched controls (30)	Tests for systemic parasympathetic and sympathetic function	To compare systemic autonomic function between the 3 groups	No systemic autonomic dysfunction in people with PACG[j]
Gugleta et al. [84]	Patients with OAG[k] and hypotension on 24 h ABPM[h] (22)	Treatment with fludrocortisone	Diurnal intraocular tension curve recordings; VF[c]; 24 h ABPM[h]	The mean BP[e] readings were higher and there was less severe nocturnal dipping on follow up 24 h ABPM[h]. Intraocular pressure and VF[c] remained stable
Demailly et al. [58]	Patients with LTG[l], OAG[k] and controls (148)	On clinical history symptoms of occlusive arterial disease; prevalence of rhythm and conduction abnormalities on the ECG[m]; mean CV[i] risk factor levels; mean orthostatic BP[e] drop	To compare the prevalence of CV[i] characteristics across the 3 groups	Mean difference of orthostatic BP[e] was significantly greater in the LTG[l] group (systolic BP[e]: −6.9 mmHg) than in the OAG[k] group (−1.2 mm HG) and the control group (−1.5 mmHg)
Bechetoille and Bresson-Dumont [85]	Patients with FIG[n] and patients with POAG[o] (32)	24 h ABPM[h]	Compared diurnal and nocturnal fluctuations in BP[e]	Patients with FIG[n] versus POAG[o] had: (1) lower DBP[p], SBP[q] and mean BP[e] over 24 h (2) lower diurnal DBP[p] and SBP[q] (3) greater nocturnal SBP[q] and a greater percentage of diurnal low readings
Galambos et al. [86]	Patients with NTG[a], POAG[o] and healthy controls (60)	PSV[r], EDV[s], and RI[t] in the SPCA[u], CRA[v] and OA[w] were recorded after a change from sitting upright to a supine body position using color Doppler imaging	Compared PSV[r], EDV[s], and RI[t] across the 3 groups	Unaltered flow velocities in the SPCA[u] of controls, suggests tight autoregulation. Flow velocities in the CRA[v] and OA[w] followed alterations in hydrostatic pressure. However those with NTG[a] and POAG[o] had insufficient compensatory response to postural change, with accelerated flow in the SPCA

[a] NTG, normal tension glaucoma.
[b] HR, heart rate.
[c] VF, visual field.
[d] OH, orthostatic hypotension.
[e] BP, blood pressure.
[f] dDP, diastolic double product.
[g] sDP, systolic double product.
[h] ABPM, ambulatory blood pressure monitoring.
[i] CV, cardiovascular.
[j] PACG, primary angle closure glaucoma.
[k] OAG, open angle glaucoma.
[l] low tension glaucoma.
[m] ECG, electrocardiogram.
[n] FIG, focal ischaemic glaucoma.
[o] POAG, primary open angle glaucoma.
[p] DBP, diastolic blood pressure.
[q] SBP, systolic blood pressure.
[r] PSV, peak systolic velocity.
[s] EDV, end diastolic velocity.
[t] RI, resistivity index.
[u] SPCA, short posterior ciliary artery.
[v] CRA, central retinal artery.
[w] OA, ophthalmic artery.

Table 2
Glaucoma and blood pressure variability.

Reference	Participants (N)	Predictor variable	Outcome	Main results
Riccadonna et al. [87]	Patients with NTG[a], with high tension POAG[b] and age-matched healthy controls (47)	24-h ABPM[c] and head-up tilt	Compare autonomic system activity and 24-h blood pressure variation across groups	Confirmed autonomic dysfunction in those with NTG[a] suggesting chronic ischaemia of the optic nerve may be a factor in pathogenesis
Mroczkowska et al. [88]	Patients with POAG[b], NTG[a], and healthy controls (58)	24-h ABPM[c], peripheral pulse-wave analysis, and carotid intima-media thickness. Retinal vascular reactivity to flicker light using dynamic retinal vessel analysis	Evaluate systemic vascular function and ocular vascular function across groups	Patients with POAG[b] or NTG[a] exhibit similar alterations in ocular and systemic circulation in the early stages of their disease process
Wierzbowska et al. [89]	Patients with NTG[a] and age matched controls (97)	Ambulatory 24-h ECG[d] and 24-h ABPM[c] HRV[e], BPV[f], diurnal and nocturnal BP[g] variables were specifically studied	Evaluate differences in BP[g] and HR[h] variability between study groups	Sympathovagal balance of autonomic nervous system in patients with NTG[a] shifted towards sympathetic activity however with no change of 24-h pattern of BPV[f] as compared to controls
Plange et al. [90]	Patients with NTG[a] and controls (79)	24-h ABPM[c]	Evaluate BPV[f] between groups	Those with NTG[a] showed increased variability of night-time blood pressure measurements compared to controls

[a] NTG, normal tension glaucoma.
[b] POAG, primary open angle glaucoma.
[c] ABPM, ambulatory blood pressure monitoring.
[d] ECG, Electrocardiography.
[e] HRV, heart rate variability.
[f] BPV, blood pressure variability.
[g] BP, blood pressure.
[h] HR, heart rate.

and nocturnal BP dipping and orthostatic hypotension, in patients with different forms of glaucoma. Relevant studies are summarised in Tables 1 and 2. The search strategy included the terms glaucoma, orthostatic hypotension, hypotension, variability, ocular hemodynamics and blood pressure. Excluded were papers without abstracts, not in English and not specifically pertaining to progression of glaucoma in context of orthostatic hypotension or autonomic dysfunction. This meant, for example, exclusion of studies investigating falls, OH and effect of medications prescribed for glaucoma.

There may also be impairment of autoregulation of retinal microcirculation in open-angle glaucoma as reduced responsiveness of the retinal vasculature to flicker light has been described in such patients [67]. In summary the literature suggests that aging, regulation of systemic and local blood flow and glaucoma are linked.

ARMD is the leading cause of impaired vision in industrialised countries [68]. There is no literature to our knowledge specifically investigating ARMD and NCVI entities such as orthostatic hypotension or autonomic dysfunction. However there is a vast literature relating to individual cardiovascular risk factors and ARMD. Consistently associated as strong and moderate risk factors include current smoking, high body mass index, history of cardiovascular disease, hypertension and raised plasma fibrinogen levels [69].

The exact location of choroidal watershed zones exhibit inter-individual variation. However, all the watershed zones of the temporal short posterior ciliary arteries meet in the submacular choroid [52]. A surrogate marker of ChBF is pulsatile ocular blood flow (POBF). A study comparing controls, patients with non exudative and exudative AMD found that POBF was lower in those with exudative AMD, which offered evidence that decreased choroidal blood flow may have a role in the development of choroidal neovascularisation in AMD [70]. Fundus angiography and other choroidal blood flow studies have shown evidence of impaired macular choroidal circulation in AMD and one study ($n = 50$) of exudative AMD has shown that choroidal neovascularisation occurred within the watershed zone in 88% of participants [71]. In a cross-sectional study of patients with non-exudative ARMD, a significant inverse correlation was observed between age and choroidal blood flow (ChBF) and blood volume but not choroidal blood velocity [72]. It has also been shown that patients with AMD who have systemic hypertension have lower ChBF compared to those who are not hypertensive [73].

In summary, the eye is a highly vascular and as such a vulnerable end organ for age-related cardiovascular disease. However the role of age-related NCVI in eye diseases is poorly studied. Thus eye pathologies and the influence of NCVI on risk and progression of such conditions merit further research.

Discussion and conclusion

The prevalence of NCVI rises with age. The underlying causes of NCVI and consequences require further study. Furthermore, the direction of causality between NCVI and end organs such as the brain and heart are unclear. For example, if NCVI is associated with impaired autoregulation in the microvasculature, this may result in impaired perfusion, oxidative stress and a 'cascade-like' effect, resulting in end-organ damage. End-organ damage in the heart and brain may further influence impaired neural regulation of the cardiovascular system and cause or exacerbate NCVI (Fig. 2). The retinal microvasculature is readily accessible to clinical assessment and may provide a 'window' into this process and changes may indicate early biomarkers of age-related cardiovascular dysfunction.

Indeed research has already suggested that the eye is a 'window to the brain'. For example, retinal microvascular changes are evident in those who have experienced lacunar stroke [74,75], and may predict risk of first time stroke [76] and risk of further vascular events following ischaemic stroke, independent of traditional risk factors or stroke subtype [77]. Retinal and choroidal changes also potentially be early biomarkers for Alzheimer's disease [78,79].

The eye may provide a 'window to the heart' [3]. Retinal vessel diameter predicts risk of coronary heart disease and in middle-aged persons [80] and changes in retinal vessel calibre

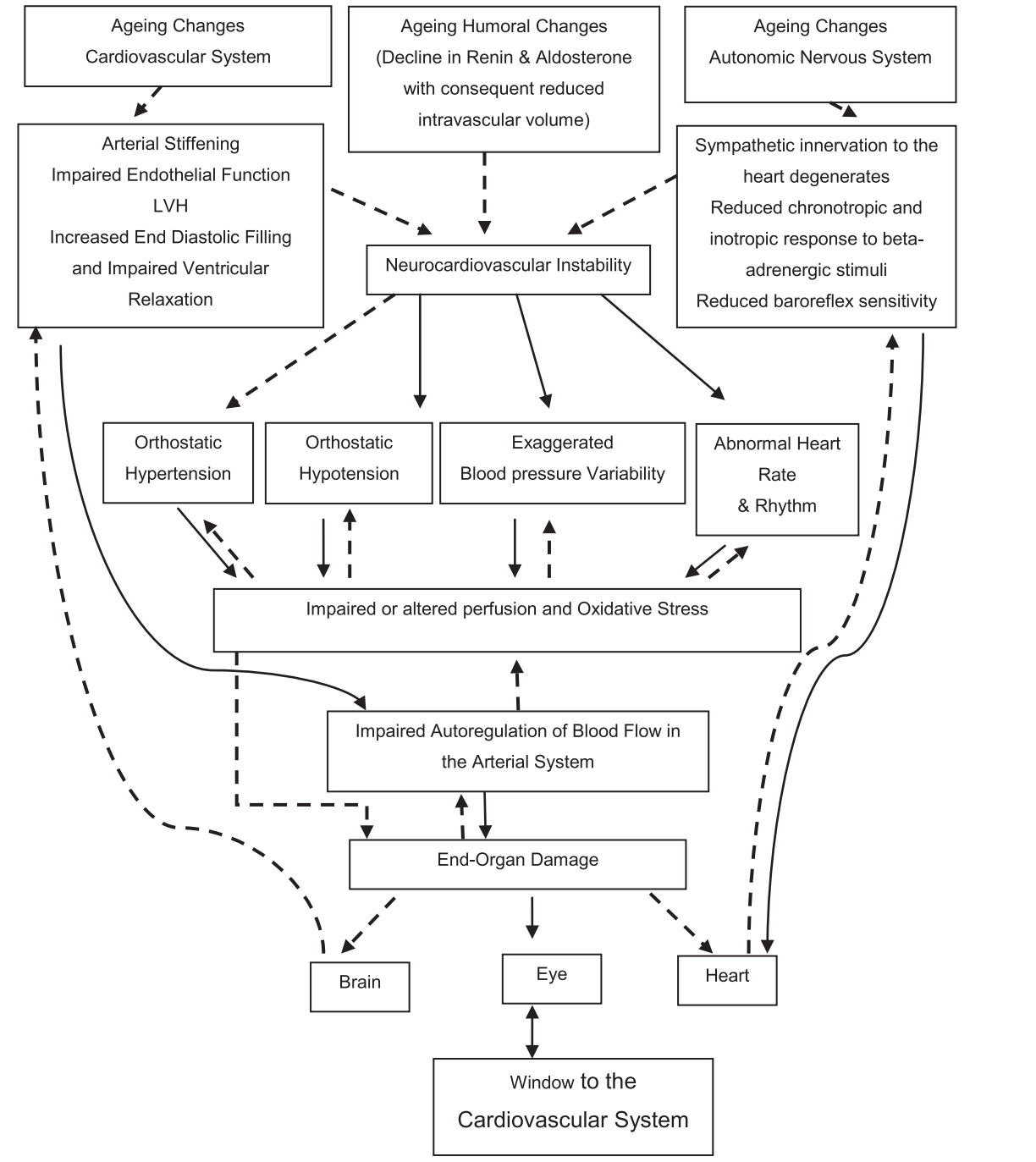

Fig. 2. The eye and neurocardiovascular instability – a working hypothesis.

and arterial stiffness correlate with peripheral hypertension [3,81]. Aortic coarctation has been associated with generalized vascular disease, but it is unknown if this is a consequence of impaired haemodynamics or an independent pathophysiological process. A recent study characterized the nature and extent of retinal vascular disease in adults with repaired aortic coarctation. They also investigated age-related effects on the former and associations with CV outcomes. Study subjects were found to have a unique retinal vascular pattern, with greater vessel tortuosity being associated with adverse CV outcomes in those 45 years or older. CV outcomes included were acute coronary syndrome, stroke, cerebral aneurysm, aortic dissection/rupture. [82]. This study supports the

view that the health of the microvasculature of the retina is linked with health of the macrocirculation.

In conclusion given that there is evidence that NCVI is associated with adverse cardiovascular outcomes including mortality; early detection of end organ involvement may inform earlier intervention for NCVI. Given that the eye is highly vascular and dependent on autonomic and vasomotor integrity; further research is required to test whether NCVI affects visual function and morphology and whether therefore the eye provides a novel access to investigate NCVI and cardiovascular pathology.

Conflict of interest

The author declares no grant support for this paper and no conflicts of interest.

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