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Review

Cardiac Dysautonomia in Huntington's Disease

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Abstract. Huntington's disease is a fatal, hereditary, neurodegenerative disorder best known for its clinical triad of progressive motor impairment, cognitive deficits and psychiatric disturbances. Although a disease of the central nervous system, mortality surveys indicate that heart disease is a leading cause of death. The nature of such cardiac abnormalities remains unknown. Clinical findings indicate a high prevalence of autonomic nervous system dysfunction – dysautonomia – which may be a result of pathology of the central autonomic network. Dysautonomia can have profound effects on cardiac health, and pronounced autonomic dysfunction can be associated with neurogenic arrhythmias and sudden cardiac death. Significant advances in the knowledge of neural mechanisms in cardiac disease have recently been made which further aid our understanding of cardiac mortality in Huntington's disease. Even so, despite the evidence of aberrant autonomic activity the potential cardiac consequences of autonomic dysfunction have been somewhat ignored. In fact, underlying cardiac abnormalities such as arrhythmias have been part of the exclusion criteria in clinical autonomic Huntington's disease research. A comprehensive analysis of cardiac function in Huntington's disease patients is warranted. Further experimental and clinical studies are needed to clarify how the autonomic nervous system is controlled and regulated in higher, central areas of the brain – and how these regions may be altered in neurological pathology, such as Huntington's disease. Ultimately, research will hopefully result in an improvement of management with the aim of preventing early death in Huntington's disease from cardiac causes.

Keywords: Huntington's disease, dysautonomia, heart disease, cardiac death, arrhythmias, heart rate variability, BDNF

INTRODUCTION

Huntington's disease (HD) is an inherited, progressive neurodegenerative disorder that results from an expanded CAG triplet repeat sequence within the huntingtin gene [1]. It is found throughout all racial groups but shows highest prevalence in the Western world, where about 7–10 individuals per 100,000 are affected [2]. Clinically, HD is characterised by progressive motor impairment, cognitive deficit, and psychiatric symptoms, most likely as a result of neuronal dysfunction and neuronal apoptosis [3–5]. In most patients HD becomes symptomatically detectable between 30 and 40 years of age, although the disorder can manifest at anytime between infancy and senescence [2, 6, 7]. There is currently no cure or effective modifying treatment for HD, and death usually occurs 15–20 years after clinical onset [8].

Although primarily a disease of the central nervous system, recent research has revealed a variety of abnormalities in peripheral tissues or organs in patients with HD [9, 10]. Whether these defects are a direct consequence of peripherally expressed mutant *huntingtin* protein, or secondary to either a general decline in health or the onset of neurological dysfunction, is yet to be fully understood. Interestingly, a review of available epidemiological and research data indicates that heart disease is the second most common cause of death in

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patients with HD, following pneumonia [11–17]. Cardiac failure is implicated in about 30% of HD patients, in contrast to less than 2% of age-matched non-HD patients in the general population [10, 18, 19]. Progressive cardiac dysfunction has also been reported in the transgenic mouse models of HD [20–23]. Nonetheless, the mechanisms of cardiac pathophysiology in HD patients remain unknown.

Transgenic HD mice have recently been studied looking for evidence of cardiac abnormalities associated with the mutant *huntingtin* expression. Poly-Q aggregate pathology has been identified in R6/2 mice and in the HdhQ150 knock-in model. Mihm et al. [20] found significant levels of mutant *huntingtin* aggregation in the nucleus and mitochondria of cardiomyocytes, which was associated with modified mitochondrial structure and myocardial atrophy in the R6/2 mouse. Left ventricular dilatation and contractile dysfunction was reported and cardiac output reduced by 50% by 12 weeks of age compared to controls [20]. In addition, generation of mice with cardiomyocyte-specific expression of poly-Q preamyloid oligomers under the control of the α-myosin heavy chain promotor lead to protein aggregate formation, necrosis, cardiac dilation, and reduced lifespan [21]. Even though these findings suggest that heart disease in HD could be a result of intrinsic cardiomyocyte dysfunction, one should be cautious in interpreting these results. The cardiac pathophysiology may be due to non-physiological levels of poly-Q, resulting from the over-expression of the protein. Thus, these transgenic mouse models might not directly mimic the situation in human HD. Indeed, in studies of the R6/1 mouse, a model displaying less aggressive and slower onset of HD symptoms, the cardiac phenotype has shown no overt histological abnormalities [23]. Moreover, there is no data to date showing expression of mutant *huntingtin* in the human heart. This might, of course, be simply due to the lack of *post mortem* specimen available for analysis. Further study of the possible cardiotoxic entities of mutant *huntingtin* in human HD tissue is warranted.

Clinical data also suggest that profound autonomic nervous system (ANS) dysfunction often accompanies HD, and this might be associated with widespread pathology of the central autonomic network [9, 24, 25]. It has thus been suggested that aberrant activity of the ANS in HD plays a role in the increased risk of succumbing to cardiac events [10, 26, 27]. The potential cardiac consequences and possible mechanisms of ANS dysfunction in HD patients have, however, received little attention.

In this brief review, we discuss the current knowledge of cardiac autonomic dysfunction in clinical and experimental models of HD. By drawing evidence from recent data within the field of HD, and other neurocardiology studies, we provide a possible explanation of the mechanisms of neurocardiac abnormalities, as well as cardiac causes of death in HD.

CARDIAC DYSAUTONOMIA IN HUNTINGTON'S DISEASE PATIENTS

Autonomic dysfunction frequently accompanies HD. Patients report of significantly more gastrointestinal, urinary, sexual and cardiovascular problems relative to age- and sex-matched controls [24]. Accordingly, clinical HD studies using various testing methods such as heart rate variability (HRV) analyses have revealed aberrant activities of both the sympathetic and parasympathetic branches of the ANS. Early data demonstrated hypofunction of the ANS in advanced HD patients [28, 29]. Using classical HRV bedside tests, Sharma and colleagues concluded from their investigation of 22 HD patients that autonomic neurocardiac regulation was characterised by an imbalance between sympathetic and parasympathetic control of the heart [29]. Similarly, decreased cardiovagal activity was found in the middle stages of HD indicated by a decline in HRV at rest and during deep respiration, both resembling vagus-dominant autonomic test conditions [26]. It is worth mentioning here that patients taking medication known to possess an anticholinergic effect were still enrolled in these studies, and this might have had an impact on the results. Spectral analysis of HRV, in contrast, advocates increased sympathetic activity in presymptomatic HD mutation carriers and mildly disabled HD patients [30]. This was in line with the clinical symptoms indicative of sympathetic dysfunction, such as orthostatic dizziness and tachycardia. Bar et al. [27] predominantly found parasympathetic dysfunction in their study of mid-stage HD patients compared with healthy subjects, with similar findings reported in a group of advanced HD patients [30].

Although the clinical data above is implying that cardiac autonomic control might become deregulated in HD, the evidence should, however, be interpreted with caution. First, the methods of the available studies were such that onset and timing of autonomic dysregulation was hard to establish and generally lacked specificity and sensitivity. Second, ANS activity was evaluated indirectly by analysis of HRV parameters on short-term

(1–10 min) electrocardiographic recordings in subjects commonly presenting with an arbitrary psychological state. Despite the HRV technique being a popular non-invasive method of testing cardiac ANS activity, this analysis has significant limitations in its interpretation, and its accuracy is highly controversial [32, 33]. In addition, the power spectrum HRV analysis only measures changes in ANS discharge and not the absolute intensity of sympathetic and parasympathetic activity. Detailed reviews on this matter have been published elsewhere [33–36].

It has been suggested that sympathovagal dysautonomia in favour of sympathetic drive could possibly result in fatal cardiac arrhythmias and/or cardiac failure and could, in turn, account for the unknown nature of heart related mortality in HD [26, 27, 37]. In general, augmented sympathetic outflow and/or decreased vagal activity is considered to be pro-arrhythmic, as evidenced by a variety of experimental models [38, 39]. A reduction in HRV and enhanced sympathetic activity is associated with increased risk of cardiovascular morbidity and mortality, and sudden cardiac death in even apparently healthy subjects [40–44].

No study has investigated the plausible cardiac consequences of dysautonomia in the HD patient population. In fact, underlying cardiac abnormalities such as arrhythmias have been part of the exclusion criteria in clinical autonomic HD research. An in dept study of cardiac function needs to be undertaken.

FINDINGS FROM TRANSGENIC MICE

Over the years, a variety of animal models for the study of HD have been developed. Transgenic mice expressing mutant forms of the *huntingtin* protein are the most commonly used models in HD research and are important for examining the pathophysiology of the disease. However, no mouse model mimics the human condition in its entirety, nor displays the degree of neurodegeneration that occurs in humans (recently reviewed in [45]). The inherent differences between human HD and experimental models must be kept in mind when interpreting any results. Nevertheless, each model supplies relevant data for the understanding of HD mechanisms.

Recently, ANS dysfunction has been reported in several transgenic lines [23, 46–48]. In the BACHD model (transgenic mouse expressing 97 glutamine repeats [49]), significant increased blood pressure and heart rate, together with a blunted baroreceptor reflex response was observed when compared to wild type controls [47]. The baroreflex plays a dominant role in maintaining overall circulatory homeostasis and short-term regulations of blood pressure by dynamic autonomic modulation of cardiac output and total peripheral resistance [50, 51]. Thus, baroreflex sensitivity is often used as a marker in the assessment of autonomic neural control of the heart. Dysregulation of this reflex may, in the long run, have a deleterious effect on cardiac function [51]. Human studies testing the baroreceptor reflex in HD have, nonetheless, generated mixed results [52, 27–29].

Telemetry recordings from different HD models including BACHD, R6/2 and R6/1 have indicated abnormalities in sleep patterns, body temperature and heart rate changes over a 12-hour light/dark cycle, and in circadian rhythm measured during 12-hour dark/dark conditions [23, 46, 47, 53]. Similar to findings in HD patients, BACHD mice displayed a decrease in HRV [47]. Compromised function of the ANS was further evident by increase in heart rate and body temperature, loss of day/night differences in the PR interval (time taken of the electrical impulse from sinus node to the atrioventricular node), as well as the decrease in the amplitude of rhythmicity in heart rate and body temperature [47].

In a recent comprehensive study, the neurocardiac phenotype in R6/1 transgenic mice, covering early (3 months old) to advanced (7 months old) stages of HD was investigated [23]. The data indicates pronounced cardiac ANS malfunction from an early HD phase. R6/1 mice displayed continuous long-term cardiac sympathetic enhancement as evidenced by increased heart rate levels and significant raised plasma levels of noradrenaline, along with a reduced content of cardiac noradrenaline at 7 months old [23]. The intra-neuronal metabolite of noradrenaline, dihydroxyphenylethylene glycol was, however, the same in R6/1 mice and controls, suggesting neuronal reuptake of noradrenaline was not altered [23]. Interestingly, similar alterations have been documented in the context of cardiac failure [54, 55]. Analysis of 24-hour telemetry ECG recordings in R6/1 mice revealed unstable and chaotic heart rhythms with a variety of arrhythmias including atrial flutter, atrial fibrillation, supra-ventricular and ventricular premature beats, episodes of ventricular tachycardia and, even, sudden cardiac death (Fig. 1A) [23]. Of note, heart rate variations were attenuated by administration of atropine, suggesting the erratic heart variations were due to augmented parasympathetic activity [23]. A hyperactive parasympathetic nervous system has also been reported in human HD, particularly in patients with juvenile HD [56].

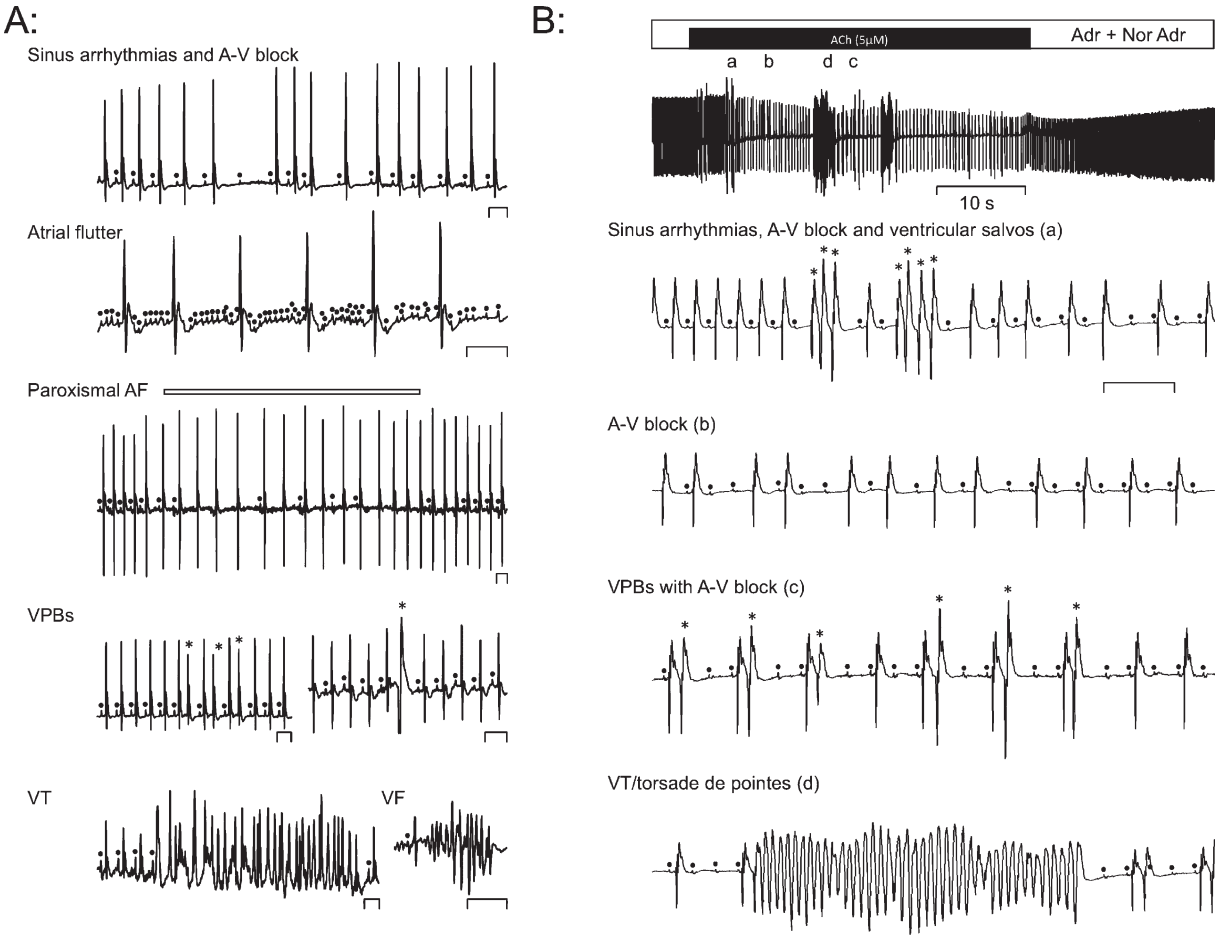

Fig. 1. Similarity of arrhythmias recorded from R6/1 mice (A) and during autonomic conflict in an isolated rat heart (B). Panel A shows ECGs recorded by telemetry from R6/1 mice. Arrhythmias include sinus arrhythmias (note absence of a consistent P-R interval), A-V block, atrial flutter, paroxysmal atrial fibrillation (AF: as indicated by the lack of P waves, unstable baseline and irregular R-R intervals) and re-entrant arrhythmias in the form of both ventricular tachycardia (VT) and ventricular fibrillation (VF). Panel B shows similar arrhythmias recorded via an epicardial electrode in a Langendorff-perfused rat heart subjected to an autonomic conflict protocol. This protocol consisted of perfusion with a constant background of adrenaline (75 nM) and noradrenaline (313 nM) on which a 1 min period of acetylcholine (ACh: 5 μM) was superimposed as indicated. The top trace shows a slow time-base recording and the arrhythmias recorded at the points marked a–d on this trace are expanded below. Solid circles indicate P waves and asterisks indicate ventricular premature beats (VPBs). The time-bars on the expanded ECG traces are 500 msec. Arrhythmias are classified according to the Lambeth Conventions II [131]. Panel A is redrawn from reference 23 and Panel B is redrawn from reference 58, by permission.

The findings of augmented sympathovagal activity leading to cardiac arrhythmias and sudden death provide new clues for possible neurocardiac causes of death in patients with HD. Similarly hyperactivity of sympathetic and parasympathetic activity is thought to play a role in sudden cardiac death after ischaemic stroke [57]. Autonomic conflict, i.e. coincidental overactivity of both limbs of the ANS, can also lead to cardiac arrest as evident by investigation of sudden death by cold water immersion [58–60]. Data from ambulatory animals have illustrated that dual sympathovagal discharges can contribute to development and maintenance of atrial flutter and paroxysmal atrial tachycardia [61–63]. Furthermore, it was recently reported that superimposing pulses of acetylcholine (to simulate burst of parasympathetic activity) on a background of moderate sympathetic drive (adrenaline-noradrenaline administration) in isolated Langendorff-perfused rat hearts produce an array of arrhythmias, such as AV block, bradycardia, tachycardia, ventricular premature beats, and a rhythm resembling life-threatening polymorphic ventricular tachycardia – torsades de pointes (Fig. 1B) [58]. The similarities between the traces in Fig. 1A and B are striking. *Ex vivo* isolated Langendorff investigation of R6/2 mice hearts has also demonstrated abnormalities

of cardiac function in form of impaired myocardial contractility and relaxability, and attenuated left ventricular developed pressure and coronary flow rate [22]. Autonomic function was, however, not investigated.

HUNTINGTON'S DISEASE BRAIN PATHOLOGY AND CARDIAC DYSAUTONOMIA

The regulation of the heart by the ANS has been widely discussed in the literature. While classical neurocardiological research on central control and regulation of cardiac functions has generally focused on parasympathetic and sympathetic circuits at the spinal and brainstem level, more recent evidence has demonstrated cardiac autonomic regulation to be under widespread cortical and subcortical influence [64, 65]. Clinical and experimental observations strongly suggest autonomic control by the prefrontal cortex, bilateral insular cortex, anterior cingulate gyrus, amygdala, and hypothalamus [66–68]. However, direct evidence linking brain pathology in HD to cardiac autonomic dysfunction is sparse. Investigations using autonomic cardiovascular challenge tests, cognitive stress (mental arithmetic) and cold pressor tests, to challenge higher-ordered ANS centres suggest dysfunction in these regions in both pre- and early symptomatic HD patients [37, 69]. These tests have, however, low sensitivity and specificity in detecting autonomic malfunction and have a variable inter-subject response [70]. Several brain regions associated with regulation of cardiac autonomic control have been found affected in the disorder [8, 71–75].

New results from the TRACK-HD study indicate significantly greater progressive grey-matter, white-matter, whole-brain, and regional atrophy in pre-manifest and early HD groups than in control groups [76]. This is in line with other data using imaging modalities and a recent coordinate-based meta-analysis for structural changes in HD based on voxel-based morphometry [77] – all demonstrating neurodegeneration in the main the components of the central autonomic network [77–80]. The insular cortex is an important region in controlling sympathovagal tone [68]. Both right and left insular lesions, often as a result of a stroke involving the middle cerebral artery, have been associated with cardiac autonomic derangement, arrhythmias and an increased risk of cardiac death [81–83]. Moreover, animal models using electrical stimulation, together with clinical data and positron emission tomography neuroimaging suggest a lateralisation of cardiac regulation in this brain region – with right insular region chiefly controlling sympathetic tone, and parasympathetic tone mediated by the left insular [57, 67, 84–88]. A noteworthy observation is the report of insular atrophy predominating in the left hemisphere in HD patients which, to some extent, may account for the sympathetic dominance and parasympathetic withdrawal demonstrated by HRV analysis in HD patients [89–91].

Known to have crucial neurotrophic functions in both the embryonic and adult brain, brain-derived neurotrophic factor (BDNF) also appears to play a major part in ANS regulation of heart rate and cardiovascular health. Humans displaying polymorphism (Val66Met) in the BDNF gene, leading to attenuated BDNF secretion, have sympathovagal imbalance [92]. BDNF and its receptor TrkB are expressed in higher cardiac control regions such as amygdala, frontal cortex and hypothalamus, along with central autonomic nuclei of the brainstem [93–97]. It was recently reported that BDNF expression protects against cardiac dysfunction via a central nervous system-mediated pathway [88]. Interestingly, levels of BDNF in the striatum, cortex, and brainstem of HD patients are reduced [99, 100]. An *in vitro* model of HD also suggests that aberrant expression of BDNF perturbs microcircuitry and signalling in the cerebral cortex, and overexpression of BDNF in the striatum ameliorates HD phenotypes in R6/1 mice [101, 102]. HD mice (N171–82Q) exhibit attenuated expression of BDNF and TrkB in brainstem cardiovascular nuclei, and also elevated heart rates and dysregulation of heart rates during restraint stress [48]. Intracerebroventricular administration of BDNF decreases and restores heart rates to wildtype levels. Future studies of HD should investigate BDNF signalling in higher autonomic cardiac control sites.

Although incompletely understood, neuronal dysfunction and neuronal cell death are also likely to be causing the neuropsychiatric symptoms associated with HD. The possible implication of psychiatric disturbances on cardiac health should not be ignored. Severe depression, anxiety, irritability, and anger are extremely common in HD patients [2, 103, 104]. Mounting evidence indicates that, in particular, depression and anxiety are risk factors for cardiac events such as coronary heart disease, atrial and ventricular fibrillation, and sudden cardiac death [105–107]. While behavioural risk factors may account for this correlation, autonomic dysregulation has been suggested to play an important role in the increased risk for cardiovascular events in patients with depressive and anxiety disorders [108].

From a broader perspective it is interesting to note that cardiac dysautonomia is a common feature of neurodegenerative disorders. Orthostatic hypotension is a frequent characteristic of parkinsonian disorders such as Parkinson's disease and multiple system atrophy and autonomic impairment has also been reported in a variety of neurodegenerative dementias [109–113]. Recent studies have revealed a high prevalence of cardiac ectopy associated with supine hypertension, baroreflex-cardiovagal failure, and baroreflex-sympathoneural failure in patients with chronic autonomic failure [114, 115] Parkinson's disease patients have also been reported to have increased mortality due to heart disease with autonomic dysregulation being suggested as a possible contributing factor [116–118].

DYSAUTONOMIA AND CARDIAC MORTALITY IN HUNTINGTON'S DISEASE – POSSIBLE MECHANISMS

The data discussed here suggest that cardiac autonomic control can become deregulated in HD. A direct link between ANS dysfunction and the cause of death in HD patients remains however tenuous. Nonetheless, it could be speculated that impairment of central autonomic cardiac control may lead to dysautonomia and autonomic conflict and, in turn, trigger heart rate instability and cardiac arrhythmias which may ultimately be lethal. Moreover, the toxic mutated *huntingtin* protein may cause *in vivo* cardiomyocyte malfunction of cardiac efficiency and perturb intracellular signalling and protein expression – all which could destabilise cardiac electrophysiology and therefore increase the susceptibility to cardiac death during autonomic imbalance (Fig. 2).

Different theories could explain the arrhythmogenic mechanism of dysautonomia, and the substrate for arrhythmias could be enhanced by various predisposing factors in HD. Sympathetic and parasympathetic stimulation, acting through beta-adrenergic and muscarinic receptors respectively, induce their effect by causing electrophysiological changes in the myocardium. Sympathetic stimulation and its resulting increase in heart rate (i.e. the R-R interval of the ECG decreases) will lead to a reduction in action potential duration and hence QT interval. In contrast, the action potential and QT interval are prolonged as the heart rate slows. Thus, on a background of increased sympathetic stimulation, co-incident parasympathetic overactivity could lead to a fair imitation of QT/RR hysteresis; that is the heart rate increases but with no accompanying decrease of the QT interval. Indeed, evidence implies that the failure of the QT interval to decrease in response to a rise in heart rate may be a feature of vagal activation [119–121]. A prolonged action potential conjoined with an increased heart rate may cause myocardial cells to be depolarised for a larger fraction of the cardiac cycle. Together with a rate-dependent rise in calcium influx, this will increase the probability of calcium overload – an established mechanism giving rise to membrane oscillations, ventricular automaticity and arrhythmias [122].

Patients with long QT syndrome (a congenital disorder with mutations in a specific potassium channel, leading to prolonged repolarisation) are highly susceptible to arrhythmias, torsades de pointes and are at increased risk for sudden cardiac death [123]. Delaying repolarisation experimentally can cause a 57-fold reduction in the diastolic interval (TQ interval) and a marked increase in the QT/TQ ratio (ECG restitution) during heart rate acceleration with sympathetic stimulation using isoproterenol challenges [124]. In other words, the ability of the heart to recover (e.g. for oxygenation and return of ion kinetics to normal state) from one beat to the next is significantly reduced, making it vulnerable to unstable re-entry and arrhythmias. Of interest, several drugs implicated in prolonging the QT interval may predispose HD patients to lethal arrhythmias. These drugs include certain antipsychotics (eg, chlorpromazine, haloperidol, thioridazine, mesoridazine) and antidepressants drugs (eg, amitriptyline, mirtazapine, citalopram), antibiotics (eg, erythromycin, clarithromycin), and gastrointestinal prokinetics (eg, cisapride, domperidone) [125].

The heterogeneity of both pre- and postsynaptic autonomic cardiac innervation may also exacerbate the pro-arrhythmic potential of dysautonomia. In normal human hearts, and those of other mammals, parasympathetic nerves and muscarinic receptors are largely located in the atria and nodel tissue. Conversely, innervation of the ventricles is predominantly by sympathetic neurons, displaying a gradient morphology with the highest density of nerve endings found at the base, decreasing to the lowest levels at the apex [126–128]. Under pathological and extreme conditions where the ANS becomes dysregulated, these regional variations may be in favour of compounding electrical inhomogeneity and trigger arrhythmias [58].

Lastly, long-standing persistent arrhythmia is a well-known cause of heart failure and cardiomyopathy and, in most cases, sudden unexpected death is caused by fatal cardiac arrhythmias [122, 129]. Any pre-existing

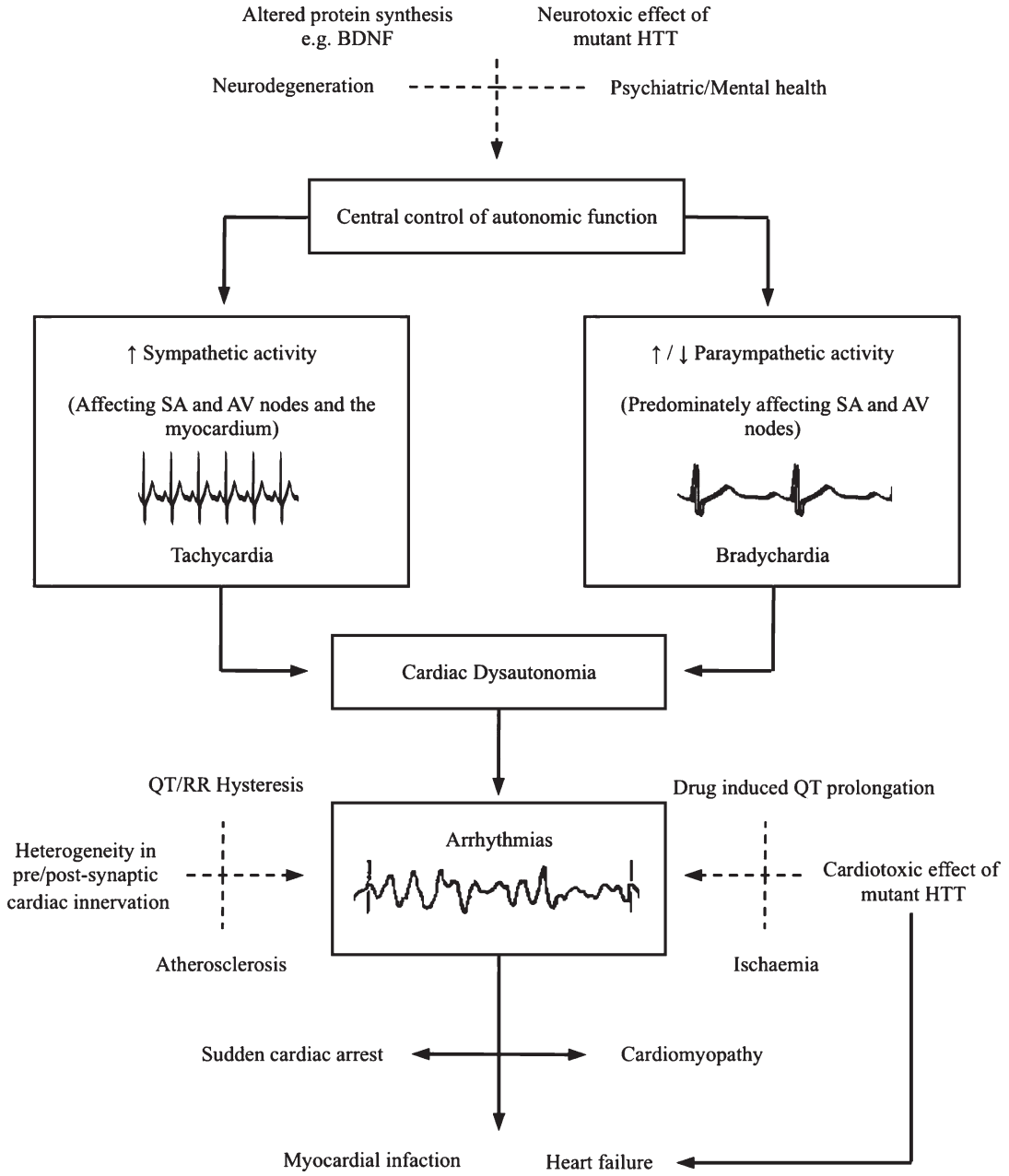

Fig. 2. Possible mechanisms of cardiac mortality from dysautonomia in Huntington's disease. The central autonomic network is likely to be affected by pathological processes and psychiatric disturbances in Huntington's disease leading to dysfunction in both limbs of the autonomic nervous system. Altered and conflicting inputs to the heart can result in arrhythmias causing cardiac dysfunction and could, ultimately, be lethal. Various predisposing factors may enhance the arrhythmogenic potential of dysautonomia. Cardiomyocyte dysfunction due to intrinsic mutant huntingtin (HTT) expression might also induce abnormalities and could directly, or in combination with altered autonomic tone, be detrimental to cardiac health. Adapted from reference 58.

coronary atherosclerotic changes or myocardial injury are also likely exacerbate arrhythmias during cardiac autonomic dysfunction. Indeed, evidence supports the role of autonomic imbalance in neurogenic myocardial injury [57, 130].

CONCLUSION AND FUTURE RESEARCH

Despite the evidence of cardiac dysautonomia in HD, the complex interactions between the brain and the heart are incompletely understood. The cause of

cardiac associated death in HD is likely to be multifactorial. Further research is needed to fully elucidate the pathophysiology and the involvement of ANS dysfunction. A detailed analysis of cardiac function in HD patients is warranted, preferably using 24 h Holter monitoring of ECG. A better understanding of cardiac electrophysiology and its interaction with sympathovagal activity is necessary. Additionally, a clarification of how the ANS is controlled and regulated in higher central areas of the brain – and how these regions may be altered by pathology – remains crucial. Functional neuroimaging and spatialtemporal mapping should allow for a better characterisation of key areas of autonomic control and alteration in HD. From a clinical perspective, this knowledge should help to identify the causative factors that make the HD heart vulnerable to cardiac events, and would also aid the development of therapeutic approaches with the aim of preventing early death from cardiac causes. Finally, a better understanding of the link between HD brain pathology and cardiac dysautonomia would also increase our knowledge of the neurogenic connections between the brain and heart.

CONFLICTS OF INTEREST

No conflicts of interest.

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