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POSITION PAPER

Pathophysiology of Takotsubo syndrome – a joint scientific statement from the Heart Failure Association Takotsubo Syndrome Study Group and Myocardial Function Working Group of the European Society of Cardiology – Part 2: vascular pathophysiology, gender and sex hormones, genetics, chronic cardiovascular problems and clinical implications

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While the first part of the scientific statement on the pathophysiology of Takotsubo syndrome was focused on catecholamines and the sympathetic nervous system, in the second part we focus on the vascular pathophysiology including coronary and systemic vascular responses, the role of the central and peripheral nervous systems during the acute phase and abnormalities in the subacute phase, the gender differences and integrated effects of sex hormones, genetics of Takotsubo syndrome including insights from microRNA studies and inducible pluripotent stem cell models of Takotsubo syndrome. We then discuss the chronic abnormalities of cardiovascular physiology in survivors, the limitations of current clinical and preclinical studies, the implications of the knowledge of pathophysiology for clinical management and future perspectives and directions of research.

Keywords Takotsubo syndrome • Pathophysiology • Vascular • Nervous system • Oestrogen • Genetics • microRNA • Inducible pluripotent stem cell models

Introduction

This is the second part of the scientific statement on the pathophysiology of Takotsubo syndrome (TTS) from the Heart Failure Association Takotsubo Syndrome Study Group and the Myocardial Function Working Group of the European Society of Cardiology. Part 1 focused upon the central role of catecholamines and the sympathetic nervous system, and the direct effects upon myocardial biology and ventricular function.[1] Here in Part 2 we focus on the vascular pathophysiology, the role of the central and peripheral nervous systems, the influence of gender and sex hormones, genetic risk, the pathophysiology of chronic cardiovascular problems in TTS survivors, current limitations of the preclinical and clinical studies to date, and future perspectives and directions for research.

Abnormalities in vascular physiology during the acute phase of Takotsubo syndrome

Coronary vasospasm, microvascular function and coronary perfusion

When Dote *et al.*[2] published their first case and coined the term 'Takotsubo cardiomyopathy', they proposed that TTS was caused by microvascular dysfunction and coronary artery spasm. Reversible perfusion defects in the affected apical segment have been documented in patients with TTS and coronary microvascular function has been reported to be diffusely impaired in TTS.[3–7] One study described the use of myocardial contrast echocardiography to measure myocardial perfusion in the affected apical segments of 15 patients with acute TTS.[8] They reported that the perfusion defect was partially reversible with adenosine infusion during the acute phase, and the defect was absent at 1-month follow-up in contrast to ST-elevation myocardial infarction (STEMI) controls where the perfusion defect was fixed, did not reduce with adenosine and was still present at 1 month post-STEMI (*Figure 1*).[8,9]

However, these reported perfusion defects were consistently observed after cardiac dysfunction had developed. It is therefore unclear whether impaired coronary perfusion causes TTS in these cases, or whether perfusion defects occurred as a consequence of TTS and reduced diastolic function given the suction wave caused by myocardial relaxation is a main contributing factor to coronary perfusion.[10,11] Isoproterenol-induced TTS-like dysfunction in the rat is not preceded by myocardial perfusion defects.[12] In addition to reduced vasodilatation and increased vasoconstriction due to autonomic system imbalance, external microvascular compression due to myocardial oedema and inflammation-related cell accumulation and to increased intracardiac pressures may contribute to the microvascular perfusion abnormalities. Myocardial oedema in the affected regions may also impair microvascular function, and reduced myocardial energy consumption secondary to cessation of contractile activities could reduce myocardial perfusion via autoregulatory mechanisms.[10,13]

Therefore, although evidence from clinical studies and some preclinical studies suggests microvascular perfusion abnormalities are present during the acute phase of TTS (*Figure 1*), whether these are primary, or secondary to myocardial dysfunction, oedema and inflammation, and how they contribute to the symptoms and pathophysiology remains to be determined.

Some investigators have previously suggested that TTS is secondary to spontaneously dissolved occlusive thrombus in one of the main coronary arteries. However, the affected myocardium in TTS typically extends beyond the perfusion territory of a single epicardial coronary artery, and intravascular ultrasound studies during acute TTS at presentation have been normal, which renders this hypothesis unlikely.[14] Furthermore long-term aspirin use does not reduce the frequency of recurrent TTS in survivors, suggesting thrombosis is not a major factor in the pathophysiology.[15]

Finally, it has been proposed that TTS might derive from epicardial coronary spasm. However, transient diffuse or segmental coronary spasm is an unlikely cause of TTS due to the following facts: (i) spontaneous or induced coronary spasm has not been documented in the majority of TTS patients, but infrequently during acetylcholine test of TTS patients at risk of endothelial dysfunction, and (ii) the topography and extent of ischaemic and metabolic ventricular defects and the distribution of regional wall motion abnormalities detected in patients with TTS do not match, and are larger than what would be expected by the coronary spasm of a single coronary artery or even by a multivessel spasm.

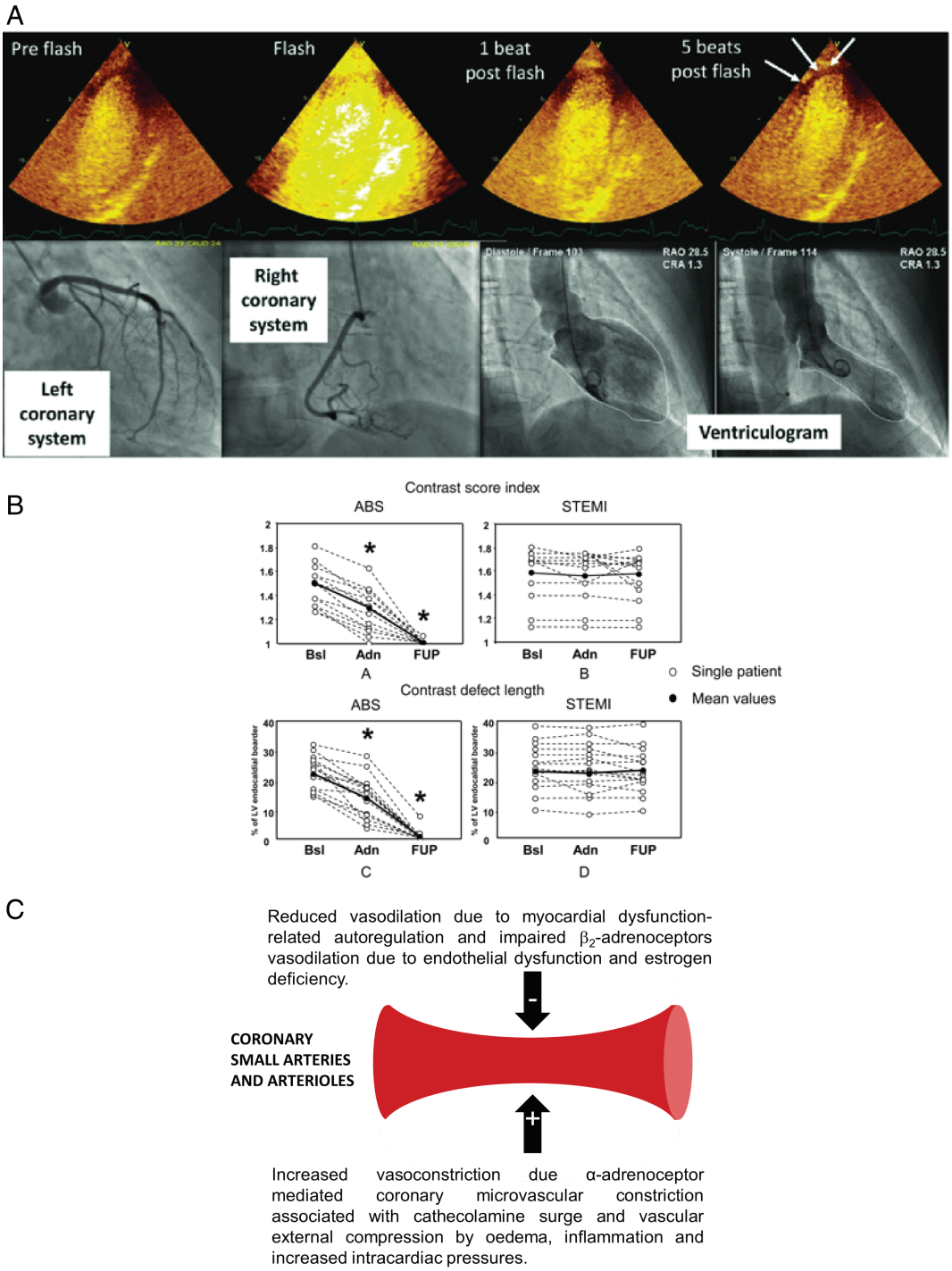

Figure 1 Pathophysiological changes in coronary microvascular function during acute Takotsubo syndrome (TTS). (*A*) Endocardial perfusion defect shown at five beats post flash in the apical myocardium corresponding to the region of hypokinesia during acute TTS using myocardial contrast echocardiography. Coronary angiography confirmed unobstructed epicardial coronary arteries (reproduced from Orde and McLean[9] with permission). (*B*) Myocardial perfusion contrast score index (*A* and *B*) and contrast defect length (*C* and *D*) at baseline (Bsl), at peak of 90 s adenosine infusion (Adn) and at 1-month follow-up (FUP) in 15 TTS and 15 ST-elevation myocardial infarction (STEMI) patients showing an acute perfusion defect in TTS patients which was partially reversible with adenosine infusion and normal perfusion at 1-month follow-up supporting a microvascular perfusion abnormality in the absence of obstructive coronary artery disease during the acute phase. *$P < 0.001$ vs. Bsl (adapted and reproduced from Galiuto *et al.*[8] with permission). (*C*) Schematic showing the various pathophysiological mechanisms leading to increased vasoconstriction and reduced vasodilatation in the coronary circulation during an acute TTS episode. ABS, apical ballooning syndrome; LV, left ventricular.

Systemic arterial regulation in the acute phase of Takotsubo syndrome

Cardiac function is closely linked and interdependent to the vascular system and ventriculo–arterial coupling,[16,17] and changes in systemic arterial function may be important in TTS.[18] Baroreflexes, which serve to maintain blood pressure by modulating responses both at the level of the heart and arteries, have been shown to be impaired in patients with TTS.[19] The sympathetic storm and catecholamine surge may lead to an acquired impairment of baroreflex control, resulting in exaggerated oscillations in blood pressure, heart rate and cardiac inotropic responses.[17] These alterations may in turn alter ventricular wall tension, and may also lead to sympathetic overactivation via other autonomic neural or endocrine feedback mechanisms.[19]

In rat models, epinephrine injection resulted in an extreme bradycardia as part of a vagal rebound response to intense vasoconstriction and arterial hypertension, and pre-treatment with atropine abolished the rebound bradycardia but did not prevent TTS.[20] Catecholamine-induced TTS-like cardiac dysfunction appears to be influenced by systemic arterial vasoconstriction or vasodilatation and is afterload-dependent, and the specific morphological TTS pattern (apical vs. non-apical) can be altered by pharmacological blood pressure lowering or raising.[21]

Patients with TTS may paradoxically have lower left ventricular end-diastolic pressures and are better haemodynamically compensated than patients with acute myocardial infarction (AMI). TTS patients more often have normal or near-normal cardiac output despite pronounced cardiac dysfunction and relatively low blood pressure.[22,23] Effects on the peripheral vasculature may contribute to the favourable prognosis in TTS, i.e. favourable ventriculo–arterial coupling may reduce afterload and improve cardiac output in the setting of significant myocardial dysfunction.[13] Although definitive studies of the status of the peripheral vasculature in TTS vs. AMI are lacking and sometimes conflicting, the presumed role of the peripheral vasculature in TTS support the hypothesis of TTS as a cardiovascular syndrome rather than solely a cardiac abnormality.

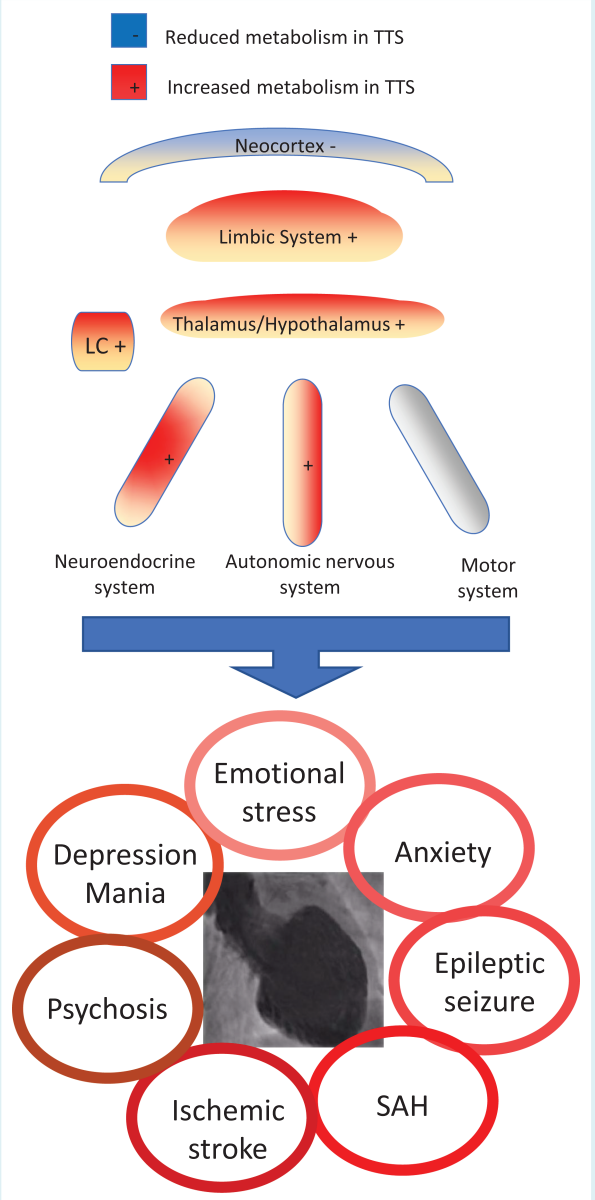

Figure 2 Changes in the central nervous system physiology during Takotsubo syndrome (TTS). The importance of the central nervous system in TTS is exemplified by the fact that some of the most common triggers of TTS are psychiatric or somatic cerebral conditions and by alterations in blood flow and metabolism in important cerebral regions in the acute phase of TTS. LC, locus coeruleus; SAH, subarachnoid haemorrhage.

The role of the central and peripheral nervous system in the acute phase of Takotsubo syndrome

Anxiety, depression and hippocampal-amygdala function in Takotsubo syndrome patients

Takotsubo syndrome is closely linked to the central nervous system via its strong association with emotional or physical stressful triggers and intense activation of the hypothalamic–pituitary–adrenal axis (*Figure 2*).[24] Acute emotional states such as psychosis, severe anxiety attacks, restraint and attempted suicide, as well as acute intracranial events such as subarachnoid haemorrhage and stroke, support an important role for the central nervous system in susceptibility to, and initiation of, TTS.[24–26] There is evidence that pre-admission anxiety disorders, but not depression, are more prevalent in TTS than in the healthy population and in patients with acute coronary syndromes.[27]

In the acute phase of TTS, neuronal glucose metabolism is altered in several cerebral regions.[28–32] Metabolism appears to increase in the hippocampus and the other components of the

limbic system, the basal ganglia, nucleus coeruleus, thalamus and hypothalamus, and the brain stem.[33] These structures are related to emotional processes and the autonomic nervous system. In contrast, metabolism appears to decrease in the pre-frontal cortex during the acute phase of TTS. Intriguingly, some of these alterations appear to persist after resolution of the acute TTS phase, i.e. after full recovery of resting cardiac function. Consistent with these findings are observations that patients with pre-existing depression or anxiety are at increased risk of developing TTS.[25,34,35] Recently the International Takotsubo Registry (InterTAK) group demonstrated hypoconnectivity of central brain regions associated with autonomic functions and regulation of the limbic system in patients with TTS. These findings suggest that autonomic-limbic integration might play an important role in the pathophysiology and contribute to the understanding of TTS.[36] Of note, not only negative emotional stress, but also positive emotions, have been suggested to trigger TTS.[37] From a pathophysiological viewpoint, it is likely that sympathetic activation may trigger coronary vasoconstriction throughout the stimulation exerted by norepinephrine and, to a lesser extent, epinephrine of alpha-adrenergic vascular receptors.[17] Finally, some evidence also exists that TTS may occur in absence of any major functional contribution from the sympathetic nervous system. This has been documented by the finding that TTS may take place in heart transplanted patients, i.e. in a clinical condition of cardiac denervation.[38,39]

There is a growing awareness that some TTS patients developed a new acquired anxiety disorder, with heightened awareness to endogenous catecholamines in scenarios of subsequent stress and sympathetic activation. Hence, potentially both chronic and acute alterations at the level of the brain appear to play a role in the pathogenesis of TTS.[24] The association between anxiety, mood disorders and TTS could also be related to the increased serum catecholamine levels induced by the use of drugs, such as serotonin–norepinephrine reuptake inhibitors, epinephrine reuptake inhibitor or lithium, as well as by the use of electroconvulsive therapy. These observations further support the consideration of TTS as a syndrome rather than merely a cardiomyopathy.

Abnormalities in the peripheral nervous system in Takotsubo syndrome

In addition to being directly involved in TTS via the control of vascular tone and systemic arterial regulation discussed above, the peripheral nervous system offers an accessible means of studying sympathetic and parasympathetic activity in the different phases of TTS.[40] However, microneurographic studies have shown somewhat conflicting results regarding peripheral sympathetic nerve activity in TTS. One study reported increased muscle sympathetic nerve activity in the acute phase among patients with TTS compared to patients with acute decompensated heart failure,[19] whereas another study reported similar muscle sympathetic nerve activity in the acute phase of TTS and lower activity in the subacute phase of TTS compared to healthy controls.[40] Further studies are required to define the role of the peripheral nervous system in its contribution to TTS initiation via intense peripheral vasoconstriction and vasodilatation, and its subsequent dysregulation during the recovery phase.

The importance of gender and sex hormones in Takotsubo syndrome pathophysiology

Ninety percent of TTS patients are female,[25,41,42] especially among those with emotional rather than physical triggers.[25] TTS is particularly common after menopause,[43] and oestrogen supplementation to female ovariectomized rats attenuated stress-induced TTS-like cardiac dysfunction.[44] The lack of oestrogen has therefore been suggested to predispose women to TTS.[43] However, the precise role of sex hormones for TTS for both women and men is not fully understood and remains an important area of investigation.

The average age of patients with TTS is around 65 years. It occurs in younger patients <50 years in about 10% of cases.[45] A substantial proportion of this subgroup are male with an increased prevalence of coexisting acute neurological and/or psychiatric disorders.[45] Of note, the prevalence of cardiogenic shock, cardiopulmonary resuscitation, the need for inotropic agent use and non-invasive and invasive ventilation was particularly high in this cohort.[45] In a previous study including a small TTS population, older age was associated with in-hospital adverse outcome. In a recently published paper including 2098 patients enrolled in InterTAK study, younger and older age were not independently associated with in-hospital mortality.[45] Conversely, elderly TTS patients (>75 years) had the highest mortality rate at long-term outcome probably due to the higher prevalence of comorbidities in older compared with younger patients.[45]

Physical triggers are significantly prevalent in man, conversely emotional triggers are less frequently detected.[46,47] Furthermore, chest pain is less common at presentation in men, who generally have a lower initial ejection fraction.[46] Differences have also been reported about outcome with higher prevalence of cardiogenic shock and mortality rate in males.[46]

Oestrogen reduces β1 (β1AR) and β2-adrenergic receptor (β2AR) expression and responsiveness, and after the menopause activation of β1AR and β2AR results in greater responses compared to matched controls.[48] There have been limited studies specifically measuring oestrogen levels in TTS patients, and they reported similar levels of oestradiol and other sex steroids among women with TTS and age-matched women with AMI.[49,50] Menopause is associated with age-related worsening of cardiovascular function, and other sex-specific differences in vascular biology that do not directly relate to sex hormones may also be important in TTS.[50,51] The importance of gender in stress responses, anxiety and panic disorder is worthy of further research to determine if oestrogen is protective or the loss of oestrogen after menopause is a risk. However, there are no studies showing that hormone replacement therapy in postmenopausal women prevent the occurrence of TTS, and some observational reports that hormone replacement therapy does not prevent TTS.[49,52,53] Conversely, using *in vitro* models, oestrogens protect cardiomyocytes from the toxic effects of high catecholamine exposure,[54] suggesting

there could be a role to prevent recurrences or complications in susceptible individuals. This is an area worthy of research requiring more detailed preclinical studies and prospective randomized clinical trials.

Another unanswered question is what the pathophysiology of TTS is in the 10% of cases who are male? For unclear reasons, TTS appears to be relatively more common among men in Japan[55] compared to Europe[56] or the United States,[57] and the male subgroup is relatively underreported and understudied. Whether biological or societal differences explain the relatively greater sex disparity in TTS incidence in Europe and the United States compared to Japan remains to be established.

Takotsubo syndrome and cancer

There is a higher rate of TTS in patients with cancer than in the general population.[58,59] In addition to the increased emotional stresses associated with the diagnosis of cancer and cancer treatments (5-fluorouracil, immune checkpoint inhibitors, vascular endothelial growth factor and tyrosine kinase inhibitors), scans and results, the pathophysiology of cancer and specific treatments may also be relevant. Many cancers are associated with both elevated sympathetic tone and inflammation, which may increase the risk of TTS. Further research is required to define the specific pathophysiological factors in cancer patients that are relevant to the development of TTS.

Insights from clinical gene expression profiling and genome studies

Several familial TTS cases have been identified[60–63] but large genetic studies of patients with TTS are lacking, with the largest study to date consisting of 96 patients with TTS.[64] The few studies that reported on the presence vs. absence of functional polymorphisms in candidate genes in TTS have reported conflicting results.[65–67] Whereas some studies reported associations between genetic variants of β1AR and β2AR and the GRK5 genes, these associations were absent in other cohorts of TTS patients.[67,68] Experimental and small clinical studies have reported TTS-associated alterations in genes related to calcium homeostasis,[69] inflammation,[70,71] innate immunity[70] and cell survival,[70,71] but all these studies have small cohorts. As discussed above, the cell survival genes that were reported to be altered in TTS have been reported to be altered in ischaemic pre-conditioning,[72,73] and therefore ischaemic pre-conditioning may be superimposed upon the catecholaminergic pre-conditioning in a 'double hit hypothesis'. There is growing evidence that some reversible cardiomyopathies, such as peripartum cardiomyopathy and alcoholic cardiomyopathy, recognize a strong genetic predisposition represented by titin gene variants.[74,75]

microRNAs in Takotsubo syndrome

A report from 36 patients with TTS from the international TTS registry detected several microRNAs (miRs) that were differentially expressed between patients with TTS and those with STEMI.[76] Cardiac enriched miR-1 and miR-133a, which when released into the bloodstream represent myocardial damage, and miRs related to emotional stress and depression (miR-16 and miR-26a), were all found to be up-regulated in the acute setting of TTS vs. control patients. The stress and depression associated miRs were also significantly higher in patients with TTS than in STEMI, although TTS patients demonstrated lower levels of miRs related to myocardial ischaemia than in STEMI.[76] A signature of all four miRs differentiated TTS patients from those with STEMI and healthy controls with a good sensitivity and specificity.[76] A recent preclinical study showed that increased miR-16 and miR-26a expression in cardiomyocytes *in vitro* and *in vivo* predisposed to catecholamine-induced negative inotropism in the left ventricular apex and positive inotropism in the left ventricular base, and TTS generation *in vivo* at lower adrenaline concentrations.[77] This raises the possibility of a pathophysiological link between pre-existing stress and depression and TTS via these miRs, and that prior neuropsychiatric stress may prime the heart to be more vulnerable to TTS generation in situations of high adrenergic stress.[77]

Confirmation of the reported TTS-specific miR signature, or identification of other robust miR signatures in larger TTS cohorts can provide important information about the pathophysiology in TTS and could prove to be an important diagnostic tool. It may also raise the intriguing hypothesis that following an acute stress, miRs released by the central nervous system could influence myocardial gene expression, perhaps activating the cardioprotective pathways to limit stress-induced myocardial injury.

Chronic cardiovascular abnormalities in Takotsubo syndrome survivors

In contrast to previous perceptions, TTS has long lasting clinical consequences, including demonstrable symptomatic and functional impairment associated with persistent subclinical cardiac dysfunction. Data derived from a large number of observational registries raise concerns about the long-term prognosis of TTS patients. The persistence of metabolic, morphological and functional abnormalities has been demonstrated by imaging methods in patients with history of TTS at distance of the acute event. Myocardial deformation and left ventricular tissue characterization were evaluated in the acute phase and at 4-month follow-up by echocardiography and cardiac magnetic resonance (CMR) imaging, respectively, in 52 TTS patients compared with 44 age- and sex-matched healthy subjects. Despite recovery of left ventricular ejection fraction at rest, significant abnormalities in systolic and diastolic indices of myocardial deformation persisted at follow-up compared with the control group (*Figure 3*). Moreover, CMR at follow-up demonstrated reduction of myocardial oedema and early development of the left ventricular microscopic fibrosis in its place.[78–81]

At long-term follow-up, persistence of cardiac symptoms along with cardiac limitations on exercise (reduced peak oxygen consumption and increased minute ventilation to carbon dioxide production slope at treadmill cardiopulmonary exercise testing) has been demonstrated in the HEROIC study.[81] Despite a normal left

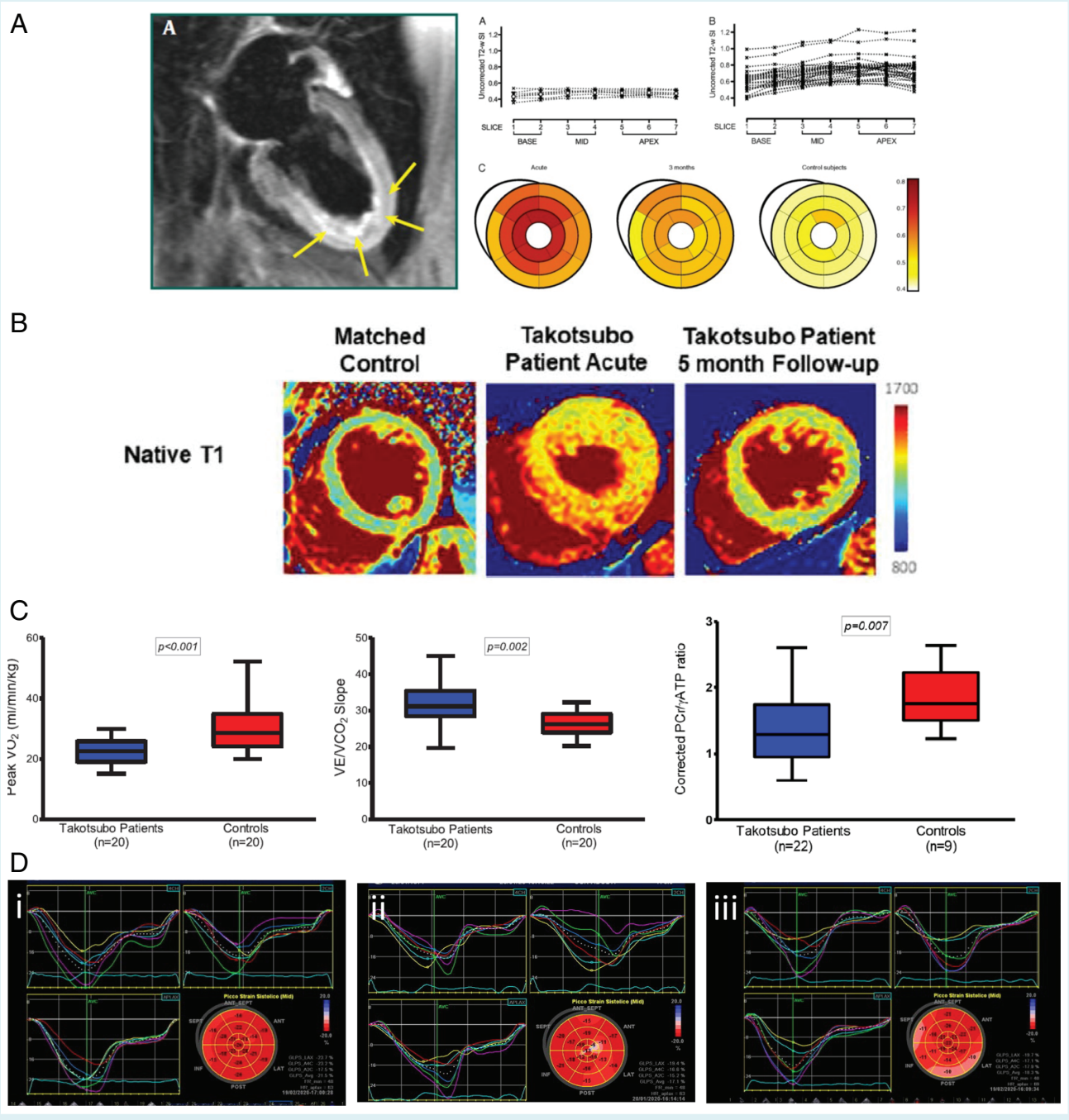

Figure 3 Chronic pathophysiological abnormalities in long-term survivors of Takotsubo syndrome (TTS). (*A*) Increased T2 STIR in the affected apical segments on cardiac magnetic resonance from cases with Takotsubo syndrome acutely and persisting at 3 months (from Neil *et al.*[79]). (*B*) Increased T1 signal on cardiac magnetic resonance during the acute phase and persisting at 6 months (adapted from Scally *et al.*[80]). (*C*) Reduced cardiopulmonary exercise performance and abnormal myocardial phosphocreatine to adenosine triphosphate (PCr/ATP) ratio and metabolism in 37 TTS patients at a minimum of 12 months (median 20 months) after the acute TTS episode compared to healthy controls [left, reduced peak oxygen consumption (VO_2); centre, increased minute ventilation to carbon dioxide production (VE/VCO_2) slope; right, reduced PCr/ATP]. Adapted from Scally *et al.*[81] (*D*) Speckle tracking curves and bull's eye: in patient with TTS and complete recovery at follow-up (i), compared to a patient with TTS and incomplete recovery of the apex at follow-up (ii), in a patient with TTS and incomplete recovery of the posterior-lateral wall at follow-up (iii).

ventricular ejection fraction at rest, patients with prior TTS had impaired cardiac deformation indices at speckle tracking echocardiography, increased T1 mapping value (implying microscopic fibrosis) at CMR and metabolic impairment in cardiac energetic status (demonstrated by reduced phosphocreatine to adenosine triphosphate ratio at 31^{P}-magnetic resonance spectroscopy).[81] A similar pattern of focal and diffuse myocardial fibrosis has been detected in patients with pheochromocytoma, suggesting that acute catecholaminergic storms may lead to comparable changes in myocardial structure and function in TTS patients.[82] Incomplete recovery is consistent with the persistence of cardiac symptoms, not reported prior to TTS onset, including angina, dyspnoea from exertion, palpitations and a state of anxiety among some patients, configuring the clinical picture of long-term heart failure phenotype. For this reason, the previous perception of TTS as a benign condition has currently been questioned abating 'the myth of rapid and complete recovery' of cardiac function in this fascinating syndrome.[83]

Limitations of current Takotsubo syndrome research studies

Limitations of clinical studies

Limitations of current clinical studies related to TTS include the absence of randomized, double-blind, placebo-controlled trials. Initially, the large registries were at a national level and retrospectively followed cohorts of patients with TTS. The TTS cohorts from the InterTAK registry[25] and the Swedish Coronary Angiography and Angioplasty Registry (SCAAR)[42] are growing each year and constitute two relatively well characterized prospective cohorts of patients with TTS.

There is also a large American cohort of patients with TTS available through the Nationwide Inpatient Sample database in the United States, although this database lacks the detail of the former registries and is dependent upon the accuracy of discharge coding.[34] The continuing accumulation of data from large TTS cohorts can allow for more robust assessment of the association between risk factors and other patient characteristics with TTS.[84,85]

Another important limitation of current clinical studies is the inconsistency in the definitions of TTS,[41,60,86–95] which complicates direct comparisons of studies that relied on different diagnostic criteria for TTS.[21] An important challenge for clinical studies that attempt to address TTS pathophysiology, which has been discussed in greater detail above, is the fact that TTS is diagnosed once the syndrome has already developed, and in some cases requires assessment at follow-up to confirm reversal of the regional wall motion abnormalities observed in the acute phase. The importance of taking into account the temporal phases of TTS should not be neglected (*Figure 4*).

It is important to be aware of the different triggers for TTS as these may influence the pathophysiology of TTS. For example, the wide spectrum of clinical presentation of TTS characterized by common phenotype associated with different clinical conditions and probably with different pathophysiological mechanisms.[96] There is a problem with the comparison of groups with homogeneous clinical and morphological characteristics in the context of a syndrome that actually accepts multiple forms. From this panorama emerges the need for a classification of the different clinical pictures that distinguishes the various subgroups even according to different molecular pathways. Some physical triggers, such as intracerebral haemorrhage and severe sepsis, are associated with systemic effects and processes that may be unrelated to TTS. It can be difficult to dissect out these TTS-unrelated factors and effects when analysing TTS cohorts consisting of patients with different TTS triggers.

In a recent publication from Sweden, 46 donor hearts (who fulfilled the European Society of Cardiology criteria for TTS), were used for transplantation.[97] After transplantation of donor hearts with TTS, left ventricular function normalized in the recipients. Neither short-term outcomes nor the composite endpoint of death or re-transplantation over time (up to 10 years) differed between recipients of donor hearts with vs. without left ventricular dysfunction.[97] This clinical study might have important impact on hypothesis generation about the pathophysiology of TTS despite being a non-randomized and relatively small observational study.

Limitations of laboratory and preclinical studies

Limitations of experimental TTS models include those common to most experimental models as well as some TTS-specific limitations. Animal experiments, which are often conducted in young healthy animals, imperfectly reflect human disease processes such as TTS, which more often occur in older subjects.[98] TTS-specific challenges include modelling the stressors that include clinical TTS. TTS-like cardiac dysfunction has been induced by subjecting rats to immobilization stress,[44] and physical stress model (somatic disease) has been shown to induce TTS-like cardiac dysfunction in an animal model. The model with the best proven reproducibility in inducing TTS-like cardiac dysfunction is based on isoproterenol administration to rats,[12,21,99,100] with the limitation that this is a pharmacological intervention that does not accurately recapitulate the effects of endogenous/paracrine catecholamines, and does not include other possible pathophysiological mechanisms or triggers, such as cerebral stress upon somatic or psychological trauma. In addition, in all these models the secondary impact of high local/paracrine cardiac catecholamine release in response to the extreme changes in haemodynamics following a catecholamine bolus or infusion is not quantified. Although useful, these models do not perfectly mimic the clinical condition and only allow for studying pathophysiological processes that occur downstream of catecholamine release.

Another important limitation is the lack of murine TTS models. Although acute regional hypo/akinesia can be induced by isoproterenol administration in mice, the typical TTS-like patterns have not been induced in mice.[101] Isoproterenol injection in mice leads to microvascular constriction and micro-infarctions, with resulting cardiomyocyte death, systolic dysfunction and reparative fibrosis, not mimicking TTS. A reliable mouse model of TTS would allow

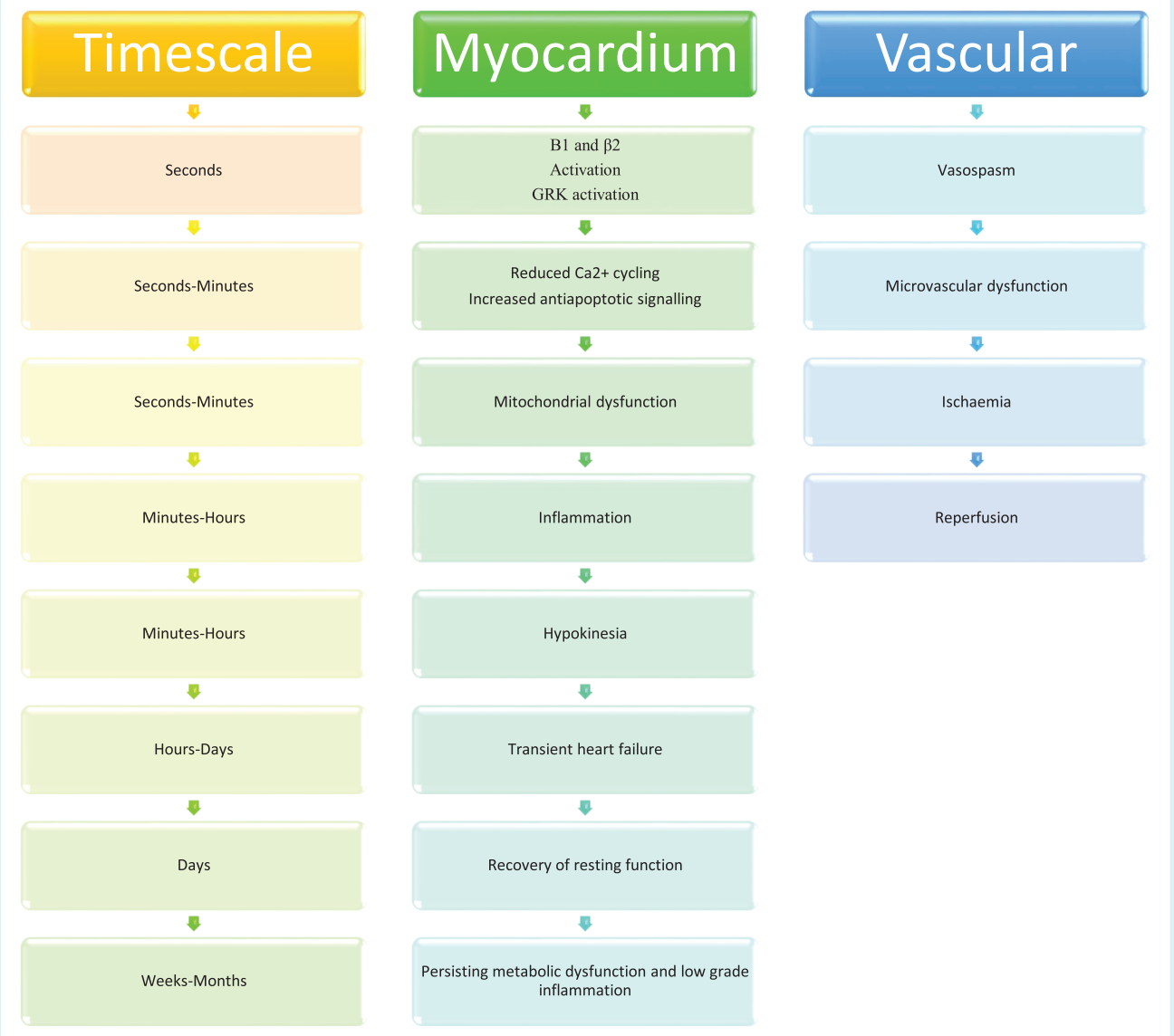

Figure 4 Temporal phases of Takotsubo syndrome pathophysiology. The different pathophysiological changes occurring in the ventricular myocardium and coronary vasculature over the timescale from seconds to months from the start of an episode of Takotsubo syndrome.

for the use of genetically engineered mouse strains, which could aid in understanding the underlying pathophysiological mechanisms and if any neurological or myocardial pathways are essential for the development of TTS.

Implications of the pathophysiology of Takotsubo syndrome on treatment recommendations

Currently, there are no evidence-based treatments for TTS during the acute phase or in the chronic phase in symptomatic patients. Insights from preclinical and clinical studies suggest catecholaminergic inotropes should be avoided, but to date no specific pharmacological or mechanical intervention has been shown to be effective. The consensus from several previous recommendations is to avoid epinephrine, dobutamine and milrinone in patients with TTS and cardiogenic shock.[88,102] Mechanical circulatory support (MCS) devices are currently recommended in the setting of acute cardiogenic shock,[103] but MCS does not directly target the underlying pathophysiology.

One pharmacological option is levosimendan, which did improve the rat TTS model when administered following high-dose epinephrine bolus.[20] A few case reports have also described recovery from cardiogenic shock with levosimendan,[104–106] but there has been no randomized controlled trial to assess the safety and efficacy of levosimendan during the acute phase for patients in

Table 1 Major priorities of research and unmet clinical needs for patients with Takotsubo syndrome

Clinical needs	Potential benefits
New tests to improve diagnostic precision of TTS on presentation and during the first 24 h of admission to hospital	Earlier diagnosis Reduce time and cost that patients are exposed to inappropriate ACS medication Reduce LoS in hospital
New treatments for TTS patients with cardiogenic shock	Reduce mortality Reduce LoS in ICU, CCU and overall hospital LoS
New treatments for TTS survivors who have long-term cardiovascular complications and symptoms reducing their QoL	Improve QoL and symptom control Reduce hospital readmission ? Reduce long-term mortality
New diagnostic strategies to identify the TTS survivors at risk of recurrence	Reduce hospital readmission Improve QoL ? Reduce mortality
New treatments to reduce the risk of recurrent TTS in patients with known recurrence or those at higher risk of recurrence	Reduce hospital readmission Improve QoL ? Reduce mortality

ACS, acute coroary syndrome; CCU, coronary care unit; ICU, intensive care unit; LoS, length of stay; QoL, quality of life; TTS, Takotsubo syndrome.

cardiogenic shock. At low doses, levosimendan increases myofilament calcium sensitivity in a catecholamine-independent manner which may be beneficial in acute heart failure such as acute TTS. However, at higher doses, it is a phosphodiesterase inhibitor which may introduce adverse effects during the acute phase of TTS, and therefore further studies are required regarding safety and efficacy in TTS and the optimal dose. Indeed, in an alternative animal model of TTS, levosimendan exacerbated isoproterenol-induced TTS-like cardiac dysfunction in rats.[107]

Conclusions and future perspectives

The biology of stress and adrenergic effects on the heart have been studied for over 100 years, but in the context of extreme stress and the effects of very high levels of catecholamines, knowledge is much more limited. TTS has opened a new field to explore the impact of high levels of stress and catecholamines on the brain and the cardiovascular system. It is complicated with multiple levels of integrated biology in the myocardium, including receptor biology, signalling pathways, mitochondrial function, inflammation, metabolism, gene expression and electrophysiology. All these changes within the heart need to be integrated at a systems biology level with peripheral vasculature, the brain, autonomic and peripheral nervous system, limbic system and hypothalamic–pituitary–adrenal axis. How changes in some or all of these systems converge to produce TTS remains the challenge for further research. Identification of the key nodal pathways in the heart, vasculature and brain which could be targets for new treatments will hopefully address the clinical unmet diagnostic and therapeutic needs during the acute phase and in chronic TTS survivors (*Table 1*). These studies must be performed carefully, with relevant preclinical models, and assurance that interference with the underlying biological pathways results in benefit and not harm.

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