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The COVID-19 System: A Translational Meta-Synthesis for Cardiac Rehabilitation and Prevention

Wolfgang Mastnak[1,2*]

[1]Research Centre for Arts Therapies, Beijing Normal University, Beijing, China
[2]Austrian Heart Association (Österreichischer Herzverband), Austria

Abstract

Objectve: During the COVID-19 era patients in long-term cardiac rehabilitation experience loneliness and suffer depressive feelings. Moreover, they are confronted with a decline in cardio-respiratory fitness, changes in eating and drinking behaviour, as well as mental stress and multiple anxieties. A wealth of research identified cardiac patients as a distinct COVID-19 risk population, as well as cardiological complications and sequelae of SARS-CoV-2 infection, impacts of measures to control the COVID-19 pandemic on heart patients are underrepresented and research is needed.

Methods: The present systemic meta-synthesis refers to evidence based medicine, microbiological research and data from personalised narrative medicine (Austrian Heart Association). These include (i) cardiovascular diseases as a risk factor of COVID-19, (ii) cardiological complications of COVID-19, (iii) psycho-social and behavioural risk factors of cardiovascular conditions, particularly of hypertension and atherosclerosis, (iv) impacts of measures to control the COVID-19 pandemic on mental health, cardiorespiratory function, life-style and quality of life in cardiac patients (long-term cardiac rehabilitation) and (v) narrative psycho-cardiological case studies during the COVID-19 year 2020. With a clear focus on translational objectives, the present meta-synthesis is designed to identify specific risk clusters, encourage adequate interventions and shed light on potentially harmful political and public health measures.

Results: Political measures to control the COVID-19 pandemic have a multiple and potentially harmful impact on cardiac patients in long-term rehabilitation as well as on a wider risk population. This comprises (i) insufficient or lacking physical exercise (e.g. caused by prohibited heart sports groups) and adverse effects on cardiorespiratory fitness and blood pressure, (ii) loneliness and the development of depressive traits alongside related psycho-cardiological threats, (iii) mental stress and pervasive anxieties along with experienced panic-mongering and the impression of being at the mercy of unpredictable political decisions, (iv) changes in eating and drinking behaviour as well as a tendency to alcoholism and substance abuse, (v) decreased (patient) empowerment, self-reliance and self-value, as well as changes in personality traits such as identity and dissociative issues and/or tendencies towards avoidant or dependent personality disorder.

Conclusion: Current political, public health and poly-pandemic conditions are complex and four major challenges can be identified: (i) politicians need reliable support from up-to-date medical research to avoid harmful decisions and to provide optimised public health measures, (ii) medical research has to promote systemic translational studies and be aware of limitations of standardised research designs in evidence based medicine such as mono-dimensional input-outcome effect sizes, (iii) domains such as long-term cardiac rehabilitation have to re-design and develop models, e.g. self-administered heart sports at home alongside remote cardiological control, for application under specific conditions such as lockdown and forced social distancing and (iv) comprehensive (epidemiology, psychosomatics, quality of life, social economy, ethics) preparedness for future and possibly even more aggressive pandemics.

Keywords: Cardio-respiratory fitness; COVID-19; Hypertension; Long-term cardiac rehabilitation; Medical epistemology; Mixed-methods; Psycho-cardiology; Public health systems; Quality of life

Introduction

Understanding the human being as intra-dynamic system embedded in complex bio-socio-cultural spheres elucidates how diseases can operate as mutually aggravating pathological factors, which also concern the cardiac patient in COVID-19 affected environments. A study from the Sarver Heart Center of the University of Arizona [1] discusses the COVID-19 severeness spectrum, which ranges 'from asymptomatic to mild respiratory symptoms and even potentially life-threatening cardiovascular and pulmonary complications', and the present article focuses on complex pathological interdependencies.

COVID-19 and Cardiovascular Diseases: A Novel Pathological Complex?

There is robust evidence of harmful impacts of SARS-CoV-2 on the cardiovascular system [2] and two main perspectives characterise research in this interdisciplinary field: on the one hand cardiac, e.g. arrhythmic [3], complications in COVID-19 patients, and COVID-19 as a serious complication of cardiovascular disorders on the other. Manish Bansal [4] comes straight to the point: 'Many patients with ... COVID-19 have underlying Cardiovascular (CV) disease or develop acute cardiac injury during the course of the illness. Adequate understanding of the interplay between COVID-19 and CV disease is required for optimum management of these patients', hence the need to understand underlying mechanisms [5].

There are two sides of the coin: cardiovascular complications such as myocardial injury, myocarditis, acute myocardial infarction,

***Corresponding author:** Wolfgang Mastnak, Professor, Research Centre for Arts Therapies, Beijing Normal University, Beijing, China; Email: wolfgang.mastnak@hmtm.de

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heart failure, dysrhythmias and venous thromboembolic events in COVID-19 patients [6,7] and manifest cardiovascular diseases as factors aggravating COVID-19 courses [8]: 'Patients with previous cardiovascular metabolic diseases may face a greater risk of developing into the severe condition and the comorbidities can also greatly affect the prognosis of the COVID-19. On the other hand, COVID-19 can, in turn, aggravate the damage to the heart.'

A Chinese study [9] analysed data from over 1000 patients with COVID-19 and stated that the single highest risk factor of infection was hypertension, reported in 15% of the infected sample. Moreover, among those who developed severe symptoms, the most common co-morbidity was hypertension with 23.7% and Kulkarni [10] concluded that 'emerging data from various countries most affected by coronavirus disease 2019 (COVID-19) reveal that hypertension is strongly associated with poor clinical outcomes'. Controversially, Schiffrin [11] suggested that 'it is unclear whether uncontrolled blood pressure is a risk factor for acquiring COVID-19, or whether controlled blood pressure among patients with hypertension is or is not less of a risk factor'.

Nonetheless, an Italian study [12] focused on underlying mechanisms and stated that 'when COVID-19 reaches a certain stage there is disproportionate endothelial damage that disrupts pulmonary vasoregulation, promotes ventilation–perfusion mismatch (the primary cause of initial hypoxaemia), and fosters thrombogenesis ... COVID-19 patients are less capable to counteract the progressive activation of the RAAS [Renin-Angiotensin-Aldosterone System]. The disequilibrium of AngII/ATR1 balance may be effective on the cardiovascular system once COVID-19 progresses and ACE2 reduces'. From the systemic perspective of this article, these positions are not necessarily contradictory but have to be qualified and call for holistic views – single quantitative results from evidence based medicine are not designed to adequately represent the whole, and medical epistemology gains momentum.

Comparable to high blood pressure, also atherosclerosis and clinical courses of COVID-19 are intertwined and form a dynamic pathological complex. Based on a systematic review researchers from Poland [13] suggest a correlation between inflammatory response, COVID- 19 and atherosclerosis and put into perspective that underlying links still remain unclear. Regarding this problem, the ESC Working Group for Atherosclerosis and Vascular Biology and the ESC Council of Basic Cardiovascular Science [14] pointed out that although primarily affecting the lungs, the SARS-CoV-2 virus also affects the cardiovascular system ... the vasculature is affected in COVID-19, both directly by the SARS-CoV-2 virus, and indirectly as a result of a systemic inflammatory cytokine storm. This includes the role of the vascular endothelium in the recruitment of inflammatory leucocytes where they contribute to tissue damage and cytokine release ... There is also evidence linking Endothelial Cells (ECs) to SARS-CoV-2 infection including: (i) the expression and function of its receptor Angiotensin-Converting Enzyme 2 (ACE2) in the vasculature; (ii) the prevalence of a Kawasaki disease-like syndrome (vasculitis) in COVID-19; and (iii) evidence of EC infection with SARS-CoV-2 in patients with fatal COVID-19.

And they underlined the importance of the endothelium in the underlying pathophysiology behind the clinical presentation in COVID-19 and proposed that endothelial biomarkers and tests of function (e.g. flow-mediated dilatation) should be evaluated for their usefulness in the risk stratification of COVID-19 patients: 'A better understanding of the effects of SARS-CoV-2 on endothelial biology in both the micro- and macrovasculature is required, and endothelial function testing should be considered in the follow-up of convalescent COVID-19 patients for early detection of long-term cardiovascular complications'.

With regard to a Chinese study [15] Mehra and Ruschitzka [16] focused on the inner connection between heart failure and COVID-19 and highlighted that in later stages of COVID-19 illness a hyperinflammatory state is manifest and the associated multisystemic syndrome results in elevated cytokines and dysregulated T cells with lymphopenia, coupled with marked elevations in C-reactive protein, cytokines such as Interleukin (IL) 2 and IL-6, elevated natriuretic peptides, which go hand in hand with cardiac inflammation or dysfunction and high serum ferritin: 'Pathologically, such myocardial manifestations are akin to a stress cardiomyopathy or cytokine-related myocardial dysfunction, which occurs in the setting of progressive stages of COVID-19 illness'.

Emphasising that patients with heart failure are more susceptible to COVID-19 and have, once infected, a more severe clinical course, an Italian study [17] pointed out that SARS-CoV-2 infects human cells binding to angiotensin-converting enzyme 2: 'Virus-mediated down-regulation of ACE2 may increase angiotensin II stimulation and contribute to the deleterious hyper-inflammatory reaction of COVID-19. On the other hand, ACE2 may be up-regulated in patients with cardiac disease and ... ACE2 up-regulation may increase the susceptibility to COVID-19 but may be also protective vs. angiotensin II-mediated vasoconstriction and inflammatory activation'. Broadly speaking, we are facing in inter-connected system of severe symptoms, key mechanisms and complex physiological systems, and again with regard to COVID-19 and heart failure DeFilippis [18] drew attention to a main concern of this article, the harmful factors of COVID-19 policies: 'The coronavirus-2019 (COVID-19) infection pandemic has affected the care of patients with Heart Failure (HF) who have contracted COVID-19 as well as those without COVID-19 who have been impacted by the restructuring of health care delivery'. And here translational core-issues of 'bench-to-bedside' come into play.

The Austrian Heart Association and COVID-19-Related Issues

The Austrian cardiac rehabilitation system comprises four phases or options, (i) early rehabilitation immediately after intensive care, e.g. heart surgery, (ii) intensive rehabilitation at specialised rehabilitation hospitals, duration several weeks (inpatients), (iii) intermittent rehabilitation over about one year (outpatients) and (iv) principally life-long cardiac rehabilitation provided by the Austrian Heart Association. Some patients also prefer to manage their long-term rehabilitation with their cardiologists or family doctors.

Formally, the Austrian Heart Association - in German language 'Österreichischer Herzverband - is a self-help organisation of cardiac patients providing nationwide support groups and activities according to cardiological rehabilitation and prevention standards, e.g. sports cardiological guidelines. These also include psycho-social support akin to psychological counselling as well as help to develop healthy life-styles, e.g. according to the INTERHEART-study and its updates or recent equivalents [19]. The Austrian Heart Association has a comprehensive health philosophy which also includes prevention of polymorbidity, quality of life and mutual help based on competence, self-experience, empowerment, mindfulness and empathy.

Political measures to control COVID-19 and the spread of SARS-CoV-2 encompasses lockdown and strict social distancing, hence also the prohibition against cardiac sports groups or meetings to share experiences with innovations of cardiological treatment. Individual statements in the sense of narrative medical data suggest that these measures not only stop cardio-rehabilitative and health promoting group activities but also have a multifaceted impact on the patients' health conditions, personalities and quality of life. Adequate research to explore these issues is vital and the core purpose of the present article.

Research Method

The issue how COVID-19 measures impact on the health status of heart patients is complex, involves data from different research types and should eventually improve the practice of cardiac rehabilitation and the patient's life, hence the decision to conduct a translational systemic meta-synthesis.

The model of systemic meta-syntheses (Figure 1) was inspired by the problem that in medical domains accumulated robustness of single studies are in the ascendant, while generation of ingenious new theories are on the decline. Although the pool of single data is immense, researchers – particularly in evidence based medicine – tend to not take advantage of these data's synergetic epistemological potential, which remains widely unexploited.

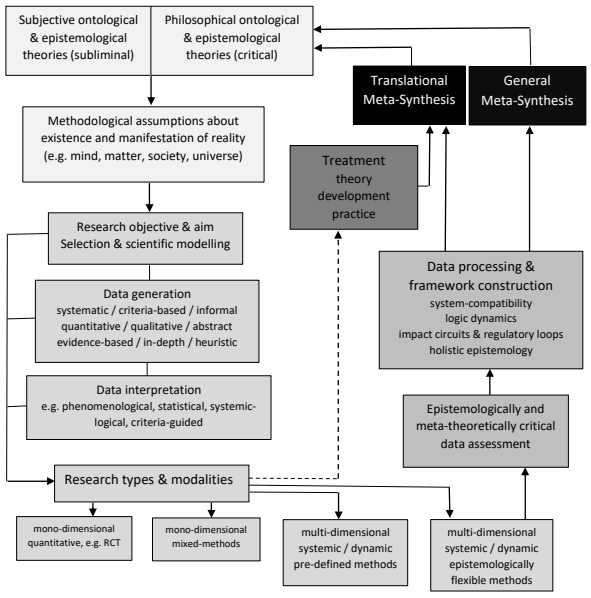

Figure 1: A translational meta-synthesis differs considerably from many standardised research models such as in evidence-based medicine: it uses epistemological methods to assess data values and creates dynamic and systemic theoretical frameworks.

In response to this deficiency, systemic meta-synthesis was designed as a model and technique to process data and findings of different characteristics, e.g. (quantitative) effect sizes in RCTs and narrative data from personalised medicine, and to unearth the inner logic of their substantial interconnections.

The present systemic meta-syntheses involves three different data-samples: (i) basically quantitative scientific findings about cardiac patients as a specific COVID-19 risk group as well as cardiological complications in COVID-19 patients, (ii) scientific findings about psychopathological and psycho-social impacts on cardiovascular diseases and (iii) narrative data from cardiac patients about experiences with COVID-19 measures and how they influence psychological, behavioural and cardiological conditions.

There are two main ways to conduct a systemic meta-synthesis: the bottom-up and the top-down mode. In bottom-up mode a broad spectrum of studies on a given issue or thematic field is taken into account and explorative comparative processing tries to trace down general principles as well as the studies' inner logic and coherence. The top-down mode starts with a given hypothesis and goes on searching for confirmatory or contradictory evidence. The present study starts at the hypothesis that COVID-19 measures may have adverse impacts on patients in long-term cardiac rehabilitation, hence the top-down mode.

Systemic meta-syntheses implicitly consider system-compatibility between their components and thus generate so called 'powered hypotheses', which also take coherence sizes into consideration. From the perspective of philosophy of science both systemic meta-syntheses and, for instance, 1A level of evidence studies in evidence based medicine are comparable. Both are based on the scientifically plausible belief in the possibility of generalisation and suggest (relatively) reliable tendencies.

The term 'translational' in the present article concerns its main focus on the patients' risks and benefits and the entire study is designed as applied research: Starting from personalised medicine and narrative data it constructs an exploratory scientific framework and concludes with focus on practical values for cardiac patients.

Harmful Protection and Cardiological Threats 'Behind the Mirror'

In his seminal book 'Behind the Mirror' original version in German language 'Die Rückseite des Spiegels' the Austrian Nobel laureate Konrad Lorenz [20] investigated culture as a living system, and his holistic and dynamic views are relevant to key issues of the present article: We have to understand the both epidemiological and socio-cultural phenomenon of COVID-19 as a system and are called to also discover the 'backside of the mirror', in other words: hidden threats of intended protection.

The pandemic of the year 2020 has brought about an interconnected epidemiological, socio-cultural, economic and political phenomenon, and conflicting approaches range from strict and long-term social distancing [21] via differentiated models such as rationally layered social distancing [22] to relatively open systems which follow other criteria such as focused protection, which is the key principle of the Great Barrington Declaration [23].

The present article suggests a systemic and epistemologically reliable view of the COVID-19 phenomenon and future pandemics, adequate translational research and public health measures which are tailored to real conditions and take also hidden threats into account. This requires systemic assessment of epidemiological dynamics, identification of vulnerable individuals and a vivid awareness of major public health concerns such as hypertension, atherosclerosis, lacking cardiorespiratory fitness and associated impacts on the immune system [24].

Physical Exercise

Sports cardiology tends to eulogise physical activity and there are very good reasons for doing so. There is robust evidence that physical activity and fitness are viable means to prevent hypertension [25,26] and cardio-sports are an efficient curative treatment of high blood pressure [27,28], even in cases of resistant hypertension [29].

Evidence based studies are complemented and substantiated by findings about underlying mechanisms such as the beneficial effects of physical exercises on oxidative stress and endothelial function [30] and a review summarises [31]: Exercise Training (ET) for Blood Pressure (BP) control has been shown to be an effective and integral component of nonpharmacological interventions for BP control. Different ET modalities (aerobic, resistance, and concurrent training) have contributed differently to BP reduction and control, driving scientific discourse regarding the optimum ET prescription (modality, volume, and intensity) for such effects; ET results in a multitude of physiological effects, with vascular and autonomic adaptations providing major contributions to BP control.

Nonetheless, practitioners in cardio-rehabilitation and particularly heart-patients in long-term cardiac rehabilitation such as members of the Austrian Heart Association are confronted with the question about possible risks and associated worries, and training intensity is considered a key issue. There is evidence [32] that high-intensity interval training and isometric resistance training have strong CV protective effects and exercise prescriptions are provided as a guide to decrease CV risk among hypertensive people alongside the assertion that exercise is a cornerstone therapy in reducing CV risk.

This includes prevention, treatment, and control of hypertension and an Australian study explains in detail [33]: One bout of aerobic exercise and regular participation in aerobic exercise has been shown to result in a lowering of blood pressure of hypertensive individuals. Higher-intensity aerobic exercise, up to 70% of maximal oxygen consumption, does not produce a greater hypotensive effect, compared with moderate-intensity aerobic exercise. Intermittent aerobic and anaerobic exercise, however, performed at an intensity >70% of maximal oxygen uptake has been shown to significantly reduce blood pressure of hypertensive individuals. Thus, faster, more intense forms of exercise can also bring about blood pressure reduction in the hypertensive population. Compared with continuous moderate-intensity aerobic exercise, high-intensity intermittent exercise typically results in a greater aerobic fitness increase in less time and produces greater changes in arterial stiffness, endothelial function, insulin resistance and mitochondrial biogenesis.

Heart patients are likely to find such guidelines confusing and worry their training might be either inefficient or too exhausting and thus harmful. This is not only a hypertension-specific problem but also relevant to other conditions and due to its positive effects physical exercise is also called a 'potential medicine' for atherosclerosis [34]. Translational microbiological research, e.g. on how physical exercise inhibits atherosclerosis by regulating neuropeptide expressions [35], and studies on inflammatory cell production and cardiovascular inflammation [36] substantiate that sedentary lifestyles increase atherosclerosis, hence the call for guided and safe training settings.

In cardiac rehabilitation practitioners are often confronted with the problem of how to 'translate' such results and how to give patients adequate support providing individualised models, encouraging sports environments and safe exercise conditions. This is one of the key duties of the Austrian Heart Association (ÖHV) and includes a broad spectrum of activities such as 'coronary heart sports groups' which focus on cardio-respiratory fitness, musculoskeletal flexibility, body awareness and social inclusion, various outdoor activities such as hiking trips at different levels of exertion, 'dancing for the heart' and Judo for heart patients [37].

Patients who have been participating in ÖHV-sports-groups for a long time are used to self-administration of physical exercise and several remote sports activities (e.g. through Zoom meetings) try to provide sustainable practice. Notwithstanding, COVID-19 policies prohibit regular cardio-training groups and there is a critical tendency that heart patients become physically inactive and cardio-respiratory fitness levels are on the decline. This does not only affect the cardiovascular status but also other factors such as mood, social inclusion, quality of life and self-images.

Stress and Anxiety

For decades psycho-oncology has been drawing attention to the causal connection between mental stress and hypertension. According to Boone [38] 'mental stress seems clearly and inextricably linked to the development and maintenance of high blood pressure', while an even older clinical study [39] did not share the 'frequently expressed notion that tension and chronic stress predispose a population to essential hypertension'.

Such contradictory findings called for more profound explanations and already in the late 1980s Heine and Weiss [40] brought advanced systematic views into play: Based on psycho-physiological, clinical and epidemiological studies, essential arterial hypertension is considered to be a consequence of an inadequate 'person-environment fit', objectively, subjectively or both. Besides genetic predisposition, salt intake, obesity and physical inactivity, psychological factors – among them 'hyper-reactivity' of the sympathetic nervous system, predisposing behaviour patterns and stressful life-events – should be taken into account in reaching a better understanding of the causes, prediction and prevention of hypertension. It was demonstrated that a maladaptation in various functional systems, even to minor psycho-emotional stress, is an important pathogenetic link between environment, objectively defined stressors and blood pressure regulation from the earliest phases of the disease. Implications for further research and behavioural interventions, together with other lifestyle-related factors, are discussed for improving the population-based health care in cardiovascular disease.

In general, clinical research provides robust evidence that psychological stress – also together with lack of social support, anxiety and uncertainty (factors we frequently find in the context of COVID-19) – can play an essential role in the development of arterial hypertension [41,42] and a recent review particularly emphasises the clinically relevant correlation between life-related stress and high blood pressure [43]: Hypertension is a major risk factor for a number of cardiovascular diseases. Proper management of hypertension may require both pharmacological and non-pharmacological interventions. Non-pharmacological interventions help reduce the daily dose of antihypertensive medication and delay the progression from prehypertension to hypertension stage. Non-pharmacological interventions include lifestyle modifications like dietary modifications, exercise, avoiding stress, and minimizing alcohol consumption. After dietary modifications, exercise and weight loss are the second major intervention for hypertension management. Avoiding stressful

lifestyle, depression, and anxiety also help to reduce elevated blood pressure. Minimizing alcohol intake also favors the blood pressure reduction. However, lifestyle modification is a dynamic process and requires continuous adherence.

These recommendations are basically in accordance with the programmes of the Austrian Heart Association, which emphatically advocates continuous adherence – and this has been critically obstructed by Austrian COVID-19 policies. In general, mental stress not only influences hypertension but is also complexly intertwined with a broad spectrum of cardiovascular diseases. Combining history of medicine in paticular referring to the 17th century English physician and neuroanatomist Thomas Willis and newer findings an Australian study [44] suggested: Contemporary research documents the phenomenon of "triggered" heart disease, when the autonomic nervous system control of the heart by the brain goes awry, producing heart disease of sudden onset, precipitated by acute emotional upheaval. This can take the form of, variously, cardiac arrhythmias, myocardial infarction, Takotsubo cardiomyopathy and sudden death. Chronic psychological distress also can have adverse cardiovascular consequences, in the causal linkage of depressive illness to heart disease, and in the probable causation of atherosclerosis and hypertension by chronic mental stress. In patients with essential hypertension, stress biomarkers are present. The sympathetic nervous system is the usual mediator between these acute and chronic psychological substrates and cardiovascular disease.

These interconnections are also substantiated by the correlation between Post-Traumatic Stress-Disorder (PTSD) and cardiovascular diseases and a study from Yale University [45] suggested that post-traumatic stress disorder independently increases risk for early incident cardiovascular disease and cardiovascular mortality by over 50% and incident hypertension risk by over 30%. Moreover, the authors pointed out that emerging research is also demonstrating that PTSD consequent to the trauma of an acute cardiac event significantly increases risk for early recurrence and mortality.

Akin to cardiopathogenic effects of stress, epidemiological data suggest a connection between cardiovascular disorders and specific anxiety symptoms such as for hypertension and its association with panic attacks and panic disorder [46]. Moreover, Tully [47] substantiated clinical observations that anxiety disorders increase the risk for incident cardiovascular diseases and that anxiety 'holds direct relevance for uncovering mechanisms of cardiopathogenesis, developing novel therapeutic strategies, and initiating clinical interventions in the population at risk of developing heart disease, or those already diagnosed with CVD'.

Narrative data from the Austrian Heart Association support the hypothesis of a complex psychopathological response to COVID-19 measures containing depression, stress and anxiety – and these are also discussed as pathogenic factors of cardiovascular diseases [48]. Numerous studies have shown that experiences with COVID-19 are at risk to generate stress, anxiety and stress [49] and taking pathogenic reinforcement loops into account, considerable cardiovascular and mental harm in cardiac patients is likely and finding solutions is one of the major challenges faced by psycho-cardiological care during the COVID-19 era.

Isolation and Depression

Although social psychology and social psychiatry distinguish between loneliness and social isolation, research suggests an important overlap between both, as well as their significant and unique association with depressive symptoms [50]. Moreover, the complex consisting of social isolation, loneliness, mental stress and depression is often experienced as a heavy burden and affects all ages, young people [51] as well as the older generation [52].

There is robust psycho-oncological evidence of causal connections between depression and cardiovascular diseases. Raič [53] called depression and cardiovascular diseases 'bidirectional related conditions' and pointed out that 'risks are for each other, and they often co-exist': Depression has a direct effect on the pathophysiological changes of various organ systems, changing the values of blood pressure, heart rate, vasomotor tone, vascular resistance, blood viscosity and plasma volume. The potential mechanism for developing heart disease in depressed patients includes hypothalamic-pituitary-adrenal gland dysfunction, increased proinflammatory and prothrombotic factor activity, reduced omega-3 fatty acids, reduced heart rate variability, smoking, physical inactivity, reduced mood, self-esteem and self-efficacy.

In this context, Seligman and Nemeroff [54] spoke about the 'interface of depression and cardiovascular disease' and Halaris [55] drew attention to the inflammation-associated co-morbidity between depression and cardiovascular disease and spoke of bidirectional co-morbidity and multifaceted underlying mechanisms:

Specific pathophysiologic factors across these systems include homeostatic imbalance between the sympathetic and the parasympathetic systems with loss of Heart Rate Variability (HRV) in depression, sympathoadrenal activation, Hypothalamic-Pituitary-Adrenal (HPA) axis activation, immune system dysregulation resulting in a pro-inflammatory status, platelet activation, and endothelial dysfunction. These abnormalities have been demonstrated in most individuals diagnosed with Major Depressive Disorder (MDD), Bipolar Disorder (BPD) ... Endothelial dysfunction has been detected in depression and may prove to be a trait marker for this illness. Thus understanding vascular biology in conjunction with psychiatric co-morbidity will be of critical importance.

Particularly with regard to underlying molecular mechanisms of how CVD is induced by loneliness and social isolation, a German study [56] emphasised that social and demographic changes have led to an increased prevalence of loneliness and social isolation in modern societies and population-based studies demonstrated that both social isolation and loneliness are correlated with a higher risk of mortality 'and that both are clearly risk factors for cardiovascular disease'.

Partly contradictory to the German results, a British study [57] highlighted the difference between objective social isolation and emotionally experienced loneliness, and showed that only loneliness was associated with an increased risk of cardiovascular disease. Social isolation, meanwhile, was not associated with disease incidence. And the authors concluded that loneliness is associated with an increased risk of developing coronary heart disease and stroke, independently of traditional cardiovascular disease risk factors and suggested that primary prevention strategies targeting loneliness could help to prevent cardiovascular disease.

These outcomes are consistent with our findings that the mental interpretation of social isolation is a crucial factor which decides, for instance, between the deep joy of meditation in seclusion and the devastating experience of abandonment, of being banned from

social participation and consigned to oblivion. In this context we also discovered the phenomenon of a unique form of re-adjustment and coping with these conditions and the question arises whether it should be considered pathological or beneficial: Individuals change their attitudes toward the world, their life philosophies and self-concept and make friends with being alone. However, there are some indications that such changes might reduce the cardiovascular risks of loneliness.

Measures to control the COVID-19 pandemic enormously involve social distancing and trigger social isolation and the experience of loneliness and Banerjee and Rai [58] summarise: 'The modern world has rarely been so isolated and restricted ... People are forced to stay at home and are burdened with the heft of quarantine. Individuals are waking up every day wrapped in a freezing cauldron of social isolation, sheer boredom and a penetrating feeling of loneliness'.

With regard to the COVID-19 era, Hwang et al. [59] pointed out that loneliness is associated with various physical and mental repercussions including elevated systolic blood pressure and increased risk for heart disease, and referring to Heffner [60] and Steptoe [61] they brought to mind that loneliness and social isolation have been associated with an increased risk for coronary artery disease associated death, even in middle-aged adults without a prior history of myocardial infarction. Furthermore, research suggested that both loneliness and social isolation are independent risk factors for higher all-cause mortality [62].

Scientific findings about loneliness and social isolation in the COVID-19 era are widely consistent with narrative data from heart patients in long-term cardiac rehabilitation (Austrian Heart Association) who are used to the supportive effect of mutual help, encouraging heart sports, empowerment and rich social participation. In this context patients posed the question whether COVID-19 measures were appropriate or if the 'collateral damage' of these measure was higher than the epidemiological benefit. Without a doubt, this is a highly complex issue which requires systemic and interdisciplinary research and in some cases political decisions look too simplistic and not consistent with the entire objectives of public health.

Obesity and Metabolic Syndrome

Obesity has become a global threat and Blüher [63] pointed out that during the past 50 years the prevalence of obesity has been constantly growing and reached 'pandemic levels'. Obesity is not only associated with unemployment, social disadvantages and reduced socio-economic productivity, but also 'substantially increases the risk of diseases such as type 2 diabetes mellitus, fatty liver disease, hypertension, myocardial infarction, stroke, dementia, osteoarthritis, obstructive sleep apnoea and several cancers, thereby contributing to a decline in both quality of life and life expectancy'. Reasons are complex and involve what Meldrum called an 'obsogenic environment' [64] including cheap calorie dense food, technologies and structure of communities which reduce or replace physical activity, and inexpensive nonphysical entertainment – and a representative index is given: 38% of American adult women are obese.

Obesity is inextricably linked with the metabolic syndrome [65] and the impact of both on the immune system [66] causes particularly in times of viral pandemics multiple detrimental effects. Analysis of clinical data [67] gives evidence that COVID-19 not only tends to be more critical in obese individuals, but also shows that the severeness of COVID-19 depends on underlying conditions, most frequent hypertension (49.7%) and obesity (48.3%). In short, patients with cardiometabolic diseases and/or obesity/metabolic syndrome are at higher risk of severe COVID-19 and resulting complications [68], and taking the close interdependencies between obesity, hypertension, atherosclerosis and inflammation processes [69-73] into account, systemic management of viral pandemics has to control the pandemic metabolic syndrome as well.

Meldrum's term afresh springs to mind and the individual appears to be a counterpart of these 'obsogenic environments': living-spaces and people form a dynamic system and we have to regard both invariable and life-style dependent factors of obesity. Molecular genetics and genome-wide association studies [74,75] shed light on genetic tendencies for obesity in various populations, identified genetic variants predisposing to obesity, and the broad spectrum of endogenous factors such as hypothyroidism, insulin resistance and polycystic ovary syndrome becomes evident. Distinct from such conditions, obesity also depends on various behavioural characteristics and involves physical inactivity, overeating and emotional stress. At that point experiences with political measures to control COVID-19 come into play: social distancing, restriction of sports activities, lockdown, existential fear and feelings of terror.

Referring to Hensley [76] and McMenemy [77] Shah [78] pointed out that psychosocial stressors stemming from the COVID-19 pandemic and resultant stay-at-home orders may exacerbate eating disorder related triggers and present a challenging environment for individuals with anorexia nervosa, bulimia nervosa and binge eating disorder. Concerning the general population without manifest eating disorder a cross-cultural study [79] analysed 1047 replies (54% women) from Asia (36%), Africa (40%), Europe (21%) and other regions (3%) and found that COVID-19 home confinement had together with adverse impacts on physical activity a negative effect on food consumption and meal patterns such as type of food, eating out of control, snacks between meals and number of main meals.

These results are compatible with narrative medical findings of the Austrian Heart Association, and although they cannot be generalised like quantitative studies with high effect sizes and statistical power, they still mirror the mental and emotional reality of cardiac patients who are used to regular participation in multifaceted long-term rehabilitation programmes. Moreover, unhealthy eating can be interpreted as a potentially harmful attempt to cope with boredom, loneliness and 'forced inactivity'. Given that recommendations such as 'do something else' are not substantially helpful, translational and personalised medical research is called to develop rehabilitation-models which can be tailored to a patients individual profile as well as to specific social and life conditions.

Alcoholism and Substance Abuse

Discussions about the relationship between alcohol consumption and cardiovascular health and disease it very heterogeneous and involves cultural traditions, implicit excuses, ideological views and bio-medical as well as psychopathological findings. Particularly red wine plays a crucial role in this debate and a recent comparative study on red wine consumption and cardiovascular health provides essential insights [80]: Benefits from moderate alcohol consumption have been widely supported by the scientific literature and ... red wine intake has been related to a lesser risk for Coronary Heart

Disease (CHD). Experimental studies and meta-analyses have mainly attributed this outcome to a great variety of polyphenolic compounds such as resveratrol, catechin, epicatechin, quercetin, and anthocyanin. Resveratrol is considered the most effective wine compound with respect to the prevention of CHD because of its antioxidant properties. The mechanisms responsible for its putative cardioprotective effects would include changes in lipid profiles, reduction of insulin resistance, and decrease in oxidative stress of Low-Density Lipoprotein Cholesterol [81] (LDL-C).

An main argument concerns dose, consumption styles and individual predispositions [81] as well as the evidence that although the consumption of alcohol can have beneficial effects on the function of the heart and the cardiovascular system, 'ethanol chronically consumed in large amounts acts as a toxin to the heart and vasculature. The cardiac injury produced by chronic alcohol abuse can progress to heart failure and eventual death. Furthermore, alcohol abuse may exacerbate pre-existing heart conditions, such as hypertension and cardiomyopathy' [82].

All in all, there is a certain tendency towards the suggestion of a Spanish study [83] that 'moderate alcohol consumption' there is a lot of opposition to this common expression and 'drinking at low risk' was suggested for medical literature [84], especially alcoholic beverages rich in polyphenols, such as wine (particularly red wine) and beer, seems to confer cardiovascular protective effects in patients with documented CVD, as well as in healthy subjects. Particularly under viral pandemic conditions also the immunomodulatory effects of ethanol and its metabolites, in particular on the NLRP3 inflammasome pathway [85] gain momentum.

Nonetheless, despite the beneficial effects of alcohol we should not downplay its risks, neither in cardiological nor in psychiatric domains, e.g. concerning alcoholism-associated hypertension [86]. The COVID-19 dynamics have an impact on alcohol consumption: Ilora Finlay and Ian Gilmore [87] called the combination of COVID-19 and alcohol 'a dangerous cocktail', an Indian study [88] on interdependencies between COVID-19 and addiction speaks of 'two pandemics which are on the verge of collision causing major public health threat' and researchers from China and Bangladesh [89] even spoke of 'hazardous and harmful alcohol use' under COVID-19 conditions.

Narrative medical data from the Austrian Heart Association are basically compatible with these findings and suggest that COVID-19 policies including lockdown, restricted freedom of movement and social activities and experienced panic-mongering, are likely to cause changes in alcohol consumption behaviour. Underlying reasons are associated with boredom, loneliness, feelings of helplessness and 'strangulation', abandonment in the sense of 'the whole world looks at corona and forgets us heart patients' and a sense of worthlessness alongside an emerging awareness that life has lost its meaning.

Such developments are very likely to generate multifactorial pathogenic dynamics including cardiological, hepatological, neurological, psychiatric and behavioural factors and are inextricably linked with sociocultural and political conditions, hence the necessity of interdisciplinary, systemic and translational approaches.

Personality Changes and Quality of Life

There is relatively little research on how the COVID-19 pandemic influences personality traits and authors tend to cautiously interpret data [90] this novel issue needs long-term and in-depth investigations. Why the question how COVID-19 conditions influence the entire personality of a cardiac patient is of such importance to the Austrian Heart Association has closely to do with its anthropological and health philosophy.

The Austrian Heart Association is based on a theoretical framework consisting of (i) regularly up-dated research and guidelines for cardiological rehabilitation and prevention, (ii) interdisciplinary perspectives such as psycho-cardiology and psycho-neuro-endocrinology, (iii) the translational paradigm of making best use of relevant scientific results, (iv) integration of evidence based medicine, bio-medical and neuroscientific basic science, systemic medicine, personalised medicine and narrative medicine, (v) personality psychology, life-span developmental psychology and psychopathology and (vi) ethical principles of humanistic care.

In many patients who adhere to the long-term – and even life-long – rehabilitative and preventative programmes of the Austrian Heart Association the initial cardiac event along with the awareness of being subject to serious pathological dispositions and/or chronic cardiovascular diseases caused complex traumatisation alongside a detrimental impact on personality traits and self-concepts.

Facing these issues the Austrian Heart Association provides help (i) to avoid the development of a self-identity as 'from henceforth nothing else than a cardiac patient', (ii) to accept the reality of the cardiac event and to deal with the associated cardiovascular disease as a potentially controllable factor, (iii) to develop an appropriate awareness of health and to change life-styles accordingly, (iv) to achieve competence in self-administered health promoting activities and (v) to get ready to accept and to give care. In this context empowerment [91,92], mindfulness [93] and mutual support are seen as key concepts.

Steps to control the spread of SARS-CoV-2 may stand in sharp contrast to these paradigms and philosophies and are likely to be experienced as severe traumatism which does harm to one's true self, as well as to subjectively important life-styles and human rights. Such traumatisation can cause symptoms of post-traumatic stress disorder and associated adverse impact on the immune system [94].

According to narrative data there are risks experiences with COVID-19 measures give rise to 'personality metamorphoses' and bring about features akin to distinct personality disorders: (i) paranoid personality disorder such as the fear of omnipresent viral threats, (ii) schizoid personality disorder when social distancing has become a stable personality trait, (iii) borderline personality disorder which mirrors political disorientation causing intense emotions which can change quickly alongside anger and suicidal thoughts, (iv) avoidant personality disorder which tries to avoid violation of both issued and 'anticipated' rules, as well as participation in socio-cultural events, (v) dependent personality disorder as individuals have given up self-determination and blindly bow to politicians who are glorified as saviours or redeemers and (vi) obsessive-compulsive personality disorder where e.g. disinfection has become the dominant behaviour.

Such psychopathological developments are still too new to allow generalisation. Nonetheless, there are – at least on the basis of case-analyses – tendencies towards such novel and mostly mixed syndromes which not only influence the quality of life but also cardiologically relevant conditions (Figure 2).

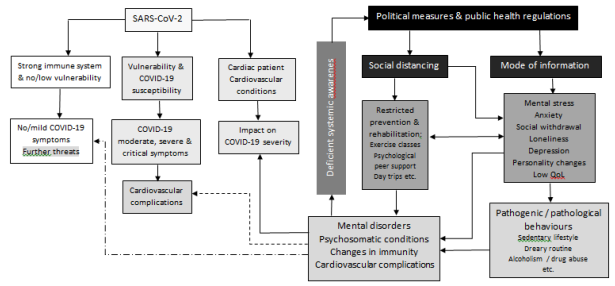

Figure 2: Measures to control the COVID-19 pandemic may entail a broad spectrum of threats. From a holistic perspective, focused protection and systemic thinking are vital for optimised public health measures.

Conclusions and Perspective

Analysing epidemiological dynamics of COVID-19, national and local health systems, as well as their bio-psycho-social interdependencies inspires the following suggestions and hypotheses:

- Cultures and countries with advanced health systems incorporate elaborated sub-systems such as in long-term cardiac rehabilitation. These are dynamic bodies equipped with inherent self-adjustment mechanisms to optimise their efficacy according to changing medical, sociocultural, climatic etc. conditions. Despite their high efficacy, these systems are usually vulnerable and fragile, not least because of their multiple interdependencies and interconnections with other systems.

- Emerging influences such as viral epidemics are likely to disequilibrate these systems and adequate re-adjustment is needed. Several COVID-19 measures and policies are basically disconnected from existing and well-working public-health-systems. Holistic re-adjustment as well as avoidance of conflicting and thus potentially harmful systems is considered a key target. Reliable and balanced assessment is required while ignoring inner dynamics of interdependent systems increases the risk that minor benefits in the one system cause major harm in the other.

- Mono-dimensional input-outcome models are not sufficient to support these processes and multi-modal and dynamic medical and public health research which also includes systemic approaches is needed. This also encompasses adequate simulation which facilitates adequate re-adjustment in emergency cases.

- Although in many medical circles SARS-CoV-2 is considered a moderate virus/viral threat and responses to infection cover a wide range from harmless to fatal – with a statistical tendency towards symptom-free and mild courses – the COVID-19 pandemic has caused considerable socio-cultural changes and immensely influenced public health systems, and it is likely that some political steps to control the pandemic do not go well with the epidemiological reality. The high regional amount of severe courses of illness might also depend on other factors such as high prevalence of obesity and low cardio-respiratory fitness, as well as associated weak immunity, hence the importance of adequate identification of risk factors, at-risk populations and focused protection.

- In several countries politicians seem to have difficulties to professionally deal with the pandemic and measures look confusing and lack scientific logic. Taking into account that COVID-19 is most probably not a singular phenomenon and the world will face further – and possibly more aggressive – public health threats, adequate emergency plans gain momentum. This requires interdisciplinary medical and public health research which also involves political sciences, system theories, philosophy of health and human rights.

Cardiology is facing new challenges which call for translational sciences and require balanced activities harmonising personalised medicine and multimodal systemic awareness.

Conflict of Interest

The Author is president of the Austrian Heart Association.

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