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Doctoral thesis

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Acute stroke and cardiovascular system. Assessment of myocardial injury with impact on patients outcome.

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Declaration:

This dissertation was created on the basis of the results obtained during my doctoral studies at the Cardiocenter, University hospital Královské Vinohrady and 3rd Faculty of Medicine, Charles University. The creation of this work was supported by the following grants: Interventional treatment of life-threatening cardiovascular diseases- INTERCARDIS",reg.no.CZ.02.1.01/0.0/0.0/16_026/0008388,   Charles University Research Programmes UNCE/MED/002,Cooperatio Cardiovascular Science, National Institute for Metabolic and Cardiovascular Disease Research (EXCELES program, reg. project number LX22NPO5104) – financed by the European Union from the Next Generation EU program. I declare that I have prepared the final thesis independently and that I have listed and cited all sources and literature used. At the same time, I declare that the work has not been used to obtain another or the same title.

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List of abbreviations

CNS	Central nervous system
ECG	Electrocardiogram
SAH	Subarachnoid hemorrhage
ICH	Intracerebral hemorrhage
AIS	Acute ischemic stroke
TIA	Transient ischemic attack
AF	Atrial fibrillation
MI	Myocardial infarction
ANS	Autonomic nervous system
ATP	adenosine triphosphate
HPA	Hypothalamic-pituitary-adrenal
NE	Norepinephrine
ISO	Isoproterenol
AC	adenylyl cyclase
PKA	Protein kinase A
cAMP	cyclic adenosine monophosphate
MAO	Monoamine Oxidase
ROS	reactive oxygen species
hs-cTnI	High-sensitive troponin I
NT-proBNP	N-terminal pro B-type natriuretic peptide
BNP	Brain natriuretic peptide
mRS	modified Rankin Scale
NSM	Neurogenic stunned myocardium

TTS	Tako-Tsubo syndrome
GDF-15	Growth differentiation factor 15
TRAIL	Tumor necrosis factor (TNF)-related apoptosis-inducing ligand
NIHSS	National Institutes of Health Stroke Scale
LBBB	Left bundle branch block
RBBB	Right bundle branch block
CRP	C-reactive protein
hsCRP	high-sensitivity C-reactive protein
DM	Diabetes mellitus
CAD	Coronary artery disease
eGFR	Estimated glomerular filtration
ER	Endoplasmatic reticulum
MAO	monoamine oxidase
CVD	Cardiovascular disease
TTE	Transthoracic echocardiography
TEE	Tranesophageal echocardiography
PFO	Patent foramen ovale
HF	Heart failure
AVP	Arginine vasopressin
AMI	Acute myocardial infarction
LVEF	Left ventricular ejection fraction
CSE	Cardiac sources of embolism
DM	Diabetes mellitus
GLS	Global longitudinal strain

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1. Introduction to Neurocardiology

1.1. History of Brain-heart interaction

The relationship between the brain and the heart has been a topic of interest for centuries. Ancient cultures such as the Greeks and Egyptians believed that the heart was the seat of the soul and emotions, while the brain was simply a cooling mechanism. It wasn't until the 17th century that the scientific study of the heart and brain began to take shape. In 1628, English physician William Harvey published his ground-breaking book "De Motu Cordis," which described the circulation of blood and the function of the heart. This laid the foundation for modern cardiovascular research. In the 19th century researchers began to study the connection between the heart and the brain. French physiologist Claude Bernard discovered that the sympathetic and parasympathetic nervous systems played a role in regulating heart rate, blood pressure, and other cardiovascular functions (1). In the early 20th century, American physiologist Walter Cannon coined the term "fight or flight" response to describe the physiological changes that occur when the body is under stress. Cannon's work helped to establish the connection between the nervous system and cardiovascular function (2).

The brain-heart connection was first described in the early 20th century. In 1901, Cushing described how increased intracranial pressure was often present with increased blood pressure and a slower heart rate. In 1914, Levy in his work showed that changes in the central nervous system (CNS) can lead to changes in cardiac function and cause arrhythmias (3). A later study from Beattie et al. showed that ventricular premature systoles can be produced by stimulating the hypothalamus (4), and in 1954, Burch et al. first described the specific electrocardiogram (ECG) patterns in 17 patients after intracranial hemorrhage, observing frequent QT interval prolongation, U waves, and large amplitude T wave (5). In the 1970s, research into the brain-heart connection began to expand. American neuroscientist Robert Ader discovered that the immune system was connected to the nervous system and could be influenced by psychological factors.

This led to the development of the field of psychoneuroimmunology, which studies the interactions between the mind, nervous system, and immune system. In the 1990s, American cardiologist Rollin McCraty founded the HeartMath Institute, which started to study the relationship between the brain and heart and their role in emotions, stress, and health. The institute has made significant contributions to the understanding of brain-heart interaction, including the discovery of the heart's own complex nervous system and the role of heart rate variability in emotional regulation and cognitive function. Subsequent studies have examined arrhythmias, repolarization and conduction abnormalities in patients after acute stroke, including subarachnoid hemorrhages (SAH), intracerebral hemorrhages (ICH), acute ischemic stroke (AIS), and transient ischemic attacks (TIA) (6-8). Today, research into the heart-brain connection continues to expand. Scientists are exploring the use of heart rate variability biofeedback as a tool for managing stress and improving cognitive function, as well as the role of the gut-brain axis in cardiovascular health. The history of heart-brain interaction research is a testament to the importance of interdisciplinary collaboration and the pursuit of scientific understanding.

1.2. Epidemiology

The Framingham study showed that post-stroke cardiovascular complications contribute significantly to illness and death (9). They manifest during the acute and chronic stages of stroke, varying in severity from minor to severe. Numerous epidemiological studies have pinpointed various risk factors associated with an elevated probability of experiencing cardiovascular complications following a stroke. Age stands out as a prominent risk factor for post-stroke cardiovascular complications. The likelihood of developing cardiovascular events rise with advancing age, and when combined with a history of stroke, this risk becomes even more pronounced. Individuals aged 65 and above, who have experienced a stroke, face a sixfold increased risk of developing cardiovascular complications compared to their counterparts without a history of stroke (10). The severity of a stroke represents another crucial risk factor. Those who undergo severe

strokes are at a higher likelihood of encountering cardiovascular complications compared to individuals with mild to moderate strokes. Furthermore, the specific location of the stroke plays a role in influencing the risk of cardiovascular complications. Several additional risk factors contribute to the occurrence of cardiovascular complications following a stroke. These encompass pre-existing cardiovascular disease, diabetes, hypertension, smoking, and dyslipidemia (9). Together, these risk factors play a role in fostering the development of atherosclerosis, a primary contributor to cardiovascular complications subsequent to a stroke.

Moreover, Framingham study showed that the incidence of stroke doubled in the presence of coronary heart disease, tripled with arterial hypertension, increased four-fold with cardiac failure, and increase five-fold with atrial fibrillation (10). Cardiovascular complications are among the leading causes of mortality after acute stroke. Cardiac events after acute stroke include myocardial infarction, heart failure, abnormal heart rhythms, and in some cases cardiac arrest. The incidence of cardiovascular events or pathological cardiac findings after acute ischemic stroke ranges from 3% for myocardial infarction to >50% for new ECG changes (11, 12). Moreover, cardiac causes are responsible for 2–6% of the mortality 3 months after an AIS, and approximately 19% of patients have a fatal or a major non-fatal cardiac event during this period (13). The most serious complications after an AIS are in the acute phase. Furthermore, impaired cardiac function after an AIS increases the risk of worse neurological outcomes and 90-day disability (14). Patients after SAH develop cardiac arrhythmias in 5% of the cases, and 80% of the patients develop ECG changes within the first year. This is also associated with a poorer outcome (8, 15).

Effective prevention of cardiovascular complications following a stroke typically requires a comprehensive approach, involving the coordination of various healthcare disciplines. This encompasses vigilant monitoring of blood pressure, lipid levels, and blood glucose levels. Lifestyle adjustments, such as smoking cessation and adopting a healthy diet, also play a crucial role in diminishing the risk of post-stroke cardiovascular complications. Moreover, healthcare providers may

prescribe medications like aspirin, beta-blockers, and statins to effectively manage these complications. In summary, cardiovascular complications following a stroke pose a significant threat to health, emphasizing the importance of factors such as age, stroke severity, and pre-existing cardiovascular conditions. Timely identification and effective management of these complications are imperative for enhancing outcomes and mitigating the long-term risk of cardiovascular disease. Moreover prevention and management of cardiac complications after stroke is critical for improving patient outcomes. Treatment strategies include anticoagulation therapy for atrial fibrillation (AF), aggressive management of hypertension and other risk factors for heart disease, and early detection and treatment of myocardial infarction (MI) and other cardiac events.

1.3.   Pathophysiology of myocardial injury

As depicted in figure 1, one of the prominent theories elucidating myocardial injury subsequent to a stroke revolves around the disruption of autonomic balance. The central nervous system plays a pivotal role in regulating autonomic responses from the brain to the heart, influencing both physiological and pathological reactions (13). Alterations in central structures directly impact the autonomic nervous system (ANS), potentially resulting in an overactive sympathetic response in the post-acute stroke phase. This connection is facilitated by sympathetic pre- and post-ganglionic neurons, leading to the activation of β-receptors and subsequent initiation of cyclic adenosine monophosphate-protein kinase A signaling. This cascade prompts the release of intracellular calcium from the sarcoplasmic reticulum, causing aberrant calcium release into the cells. This, in turn, induces contractile dysfunction, adenosine triphosphate (ATP) depletion, and mitochondrial dysfunction, ultimately resulting in reversible myocardial damage or cell death (14). Central structures that govern parasympathetic function, including the medulla oblongata, nucleus ambiguous, reticular formation, and the nucleus of nervus vagus, operate through epicardial ganglion plexuses and postganglionic nerve fibers, releasing acetylcholine. Parasympathetic activity, mediated by

muscarinic receptors, diminishes cyclic adenosine monophosphate, leading to reduced contractility by slowing depolarization. The hypothalamus, pituitary, and adrenal glands collectively form the hypothalamic-pituitary-adrenal (HPA) axis. Following an acute stroke, the adrenal glands release cortisol and activate β1 adrenoreceptors via catecholamines. This process results in excessive calcium release, ATP depletion, and oxidative stress, implying that catecholamines released into the circulation of myocardial nerve endings can potentially induce cardiac toxicity (16). Catecholamine-induced cardiotoxicity is a critical factor in stroke-induced heart injury. This toxicity arises primarily from elevated levels of catecholamines like norepinephrine (NE) and epinephrine, triggered by cerebrovascular diseases. The key pathophysiological mechanisms include myocardial ischemia, calcium overload, oxidative stress, mitochondrial dysfunction, and subsequent cellular apoptosis, fibrosis, and hypertrophy.

1.3.1. Calcium Overload

Calcium overload is a key factor in the cardiac toxicity induced by norepinephrine (NE). Elevated levels of intracellular calcium (Ca2+) have been observed in cardiomyocytes after treatment with isoproterenol (ISO), leading to the induction of cardiac apoptosis. Specifically, an increase in cytosolic ([Ca2+]i) and mitochondrial ([Ca2+]m) calcium levels occurs following prolonged catecholamine exposure, triggering harmful effects in cardiomyocytes (17-22).

1. Mitochondriocentric Signal Transducer-Effector Pathway: Mitochondrial calcium overload plays a pivotal role in cardiomyocyte death. It acts as a transducer by inducing mitochondrial oxidative stress and as an effector through the opening of the mitochondrial permeation transition pore (mPTP), leading to apoptosis and necrosis (17, 23).

2. β-Adrenergic Receptor Stimulation and Calcium Overload: β-Adrenergic receptors, part of the G-protein-coupled receptors superfamily, initiate a

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cascade upon stimulation. This cascade activates G proteins, which in turn stimulate adenylyl cyclase (AC). AC converts adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP), leading to the activation of protein kinase A (PKA) (17). PKA, a crucial serine/threonine kinase, regulates various cellular processes by phosphorylating target proteins (24, 25).

3. The activation of PKA induced by β-adrenergic receptors increases both $[Ca2+]i$ and $[Ca2+]m$. This is achieved through the phosphorylation of Ca2+-dependent proteins like L-type Ca2+ channels, sarcoplasmic reticulum ryanodine receptor Ca2+ release channels (RyR2), and phospholamban. PKA also phosphorylates troponin and myosin binding protein C, reducing their calcium affinity and resulting in increased $[Ca2+]i$ (17).

4. Role of Ca2+/Calmodulin-Dependent Protein Kinase II: Persistent β-adrenergic receptor stimulation also activates Ca2+/calmodulin-dependent protein kinase II (CaMKII) through both PKA-dependent and independent pathways (26, 27). CaMKII phosphorylates voltage-gated Ca2+ channels and RyR2 channels, leading to a further elevation of $[Ca2+]i$ (17).

5. Mitochondrial Monoamine Oxidase A (MAO-A) and Calcium Overload: MAO-A, which metabolizes NE, contributes to mitochondrial calcium overload by generating hydrogen peroxide ($H2O2$) and 4-hydroxynonenal (4-HNE) through cardiolipin peroxidation. 4-HNE then interacts with the voltage-dependent anion channel 1 (VDAC1) and mitochondrial Ca2+ uniporter (MCU), enhancing calcium transfer from the endoplasmic reticulum (ER) to the mitochondria (28, 29).

Increased $[Ca2+]i$ typically precedes a rise in $[Ca2+]m$, causing alterations in the inner mitochondrial membrane permeability. Elevated mitochondrial calcium disrupts mitochondrial respiratory functions, collapses mitochondrial membrane

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potential, and increases the production of reactive oxygen species (ROS) (17, 23, 29). In conclusion, the role of calcium overload in NE-induced cardiotoxicity is multifaceted, involving various cellular pathways and contributing significantly to the deleterious effects on cardiac cells. Understanding these mechanisms is crucial for developing targeted therapeutic interventions to mitigate NE-induced cardiac damage.

1.3.2. ROS and Oxidative Stress

Norepinephrine (NE), a key neurotransmitter in the cardiovascular system, is released by the adrenal medulla and sympathetic nerves. Its elimination involves two primary processes: reuptake (both presynaptic and extraneuronal) and metabolism. Initially, NE is converted into dihydroxyphenylglycol via oxidative deamination by neuronal monoamine oxidase (MAO). Subsequently, it undergoes O-methylation by extraneuronal catechol-O-methyl-transferase (COMT) into methoxyhydroxyphenylglycol (MHPG). This MHPG is then processed into vanillylmandelic acid in the liver and excreted in urine (17).

Emerging research highlights that catecholamine-induced cardiotoxicity is predominantly driven by the build-up of reactive oxygen species (ROS) and oxidative stress. These processes trigger a cascade of detrimental effects, including DNA damage, protein and lipid oxidation, endoplasmic reticulum (ER) stress, mitochondrial dysfunction, fibrosis, inflammation, apoptosis, hypertrophy, and lysosomal degradation (22, 30-36). While antioxidants like N-Acetylcysteine have shown efficacy in mitigating ISO-induced cardiac injury (37, 38).

Three mechanisms primarily contribute to ROS overproduction:

1. Oxidative Deamination of NE: This process, mediated by MAO, results in hydrogen peroxide (H_2O_2) formation, which is further transformed into more reactive hydroxyl radicals (OH·) through metal catalysis.

2. α1-Adrenergic Receptor Stimulation: Activates NADPH oxidase, leading to the production of superoxide anion radicals ($O_2^{-\bullet}$).

3. Formation of Aminochromes: NE oxidation results in the formation of toxic compounds known as aminochromes, occurring through a relatively slow autooxidation process that can be accelerated by ROS, redox metals, and enzymatic action (17, 39-41).

This oxidative stress induced by NE significantly burdens the cardiac cells with an overload of intracellular and mitochondrial calcium, leading to the opening of the mitochondrial permeation transition pore (mPTP). This disrupts mitochondrial membrane potential, halts oxygen transport, and contributes to cardiomyocyte depolarization (42, 43). Additionally, the "ROS-induced ROS release" mechanism further amplifies mitochondrial oxidative stress, resulting in membrane permeabilization and the release of pro-apoptotic factors (17). The rapid disruption of lysosomes due to ROS also contributes to apoptosis by releasing cathepsins (34). In conclusion, NE metabolism leads to the accumulation of reactive oxygen species (ROS), causing oxidative damage and triggering cellular apoptosis, inflammation, fibrosis, and hypertrophy.

1.3.3. Cardiac Inflammation

Systemic inflammatory responses frequently ensue in the aftermath of cerebral hemorrhages and ischemic strokes. Stroke-induced damage to plasma membranes triggers an elevation in ATP levels, initiating the activation of microglial cells and the synthesis of inflammatory cytokines. This process further stimulates oxidative stress. Inflammatory cytokines amass on endothelial cells, causing the deterioration of collagen within atherosclerotic plaques. The resultant weakening of fibrous envelopes poses a risk for coronary events (44-46). Significant inflammation has been observed in both animal models treated with ISO

and in human hearts affected by stroke and Takotsubo syndrome (47-49). Elevated markers for T cells (CD3) and macrophages (CD68) were detected in the hearts of ISO-treated mice, highlighting the inflammatory response (48). This is consistent with findings of increased HLA-DR, various cytokines, and immune cells in myocardial tissues affected by stroke (47). In Takotsubo syndrome cases, biopsies have shown myocarditis likely triggered by catecholamine release, suggesting a link between catecholamine surge and cardiac inflammation, which may further lead to fibrosis and cell death, influenced by mitochondrial ROS overproduction (50).

Inflammasome Activation in Cardiomyocytes

The β1-adrenergic receptor-stimulation-ROS pathway activates the inflammasome, crucial for cleaving pro-IL-18 and pro-IL-1β into active forms, thereby driving the inflammatory response (51-53). Chronic β-adrenergic stimulation enhances IL-18 and IL-1β mRNA expression, suggesting a sustained inflammation process (54, 55).

β2-Adrenergic Receptor Stimulation and Cardiac Fibroblasts

Stimulation of β2-adrenergic receptors in cardiac fibroblasts increases IL-6 levels, influenced by the cAMP/PKA/CREB pathway (56). In addition, ISO treatment elevates RAGE and NF-κB p65 expression, implicating the RAGE/NF-κB pathway in cardiac inflammation (57).

In summary, the cardiac inflammation response to catecholamine exposure, particularly in ISO-treated models, is multifaceted, involving various signaling pathways and cellular responses. These findings underscore the complex interplay of cellular and molecular mechanisms that drive inflammation in cardiomyocytes and cardiac tissues in response to catecholamine stress.

1.3.4. Cardiac fibrosis

Cardiac fibrosis, a detrimental consequence of catecholamine exposure, involves a network of complex signaling pathways and molecules (43, 58, 59).

1. TGF-β/Smads Pathway: The TGF-β1/Smads pathway plays a crucial role in cardiac fibrosis, as demonstrated by elevated levels of TGF-β1 and increased phosphorylation of its receptors TβRI and II in ISO-treated rat hearts. This pathway also upregulates Smads2, 3, and 4, indicating that ISO triggers fibrosis through TGF-β1/Smads signaling. Additionally, ISO treatment has been shown to enhance the activity of the Erk and Akt pathways, suggesting an involvement of the TGF-β/non-Smad pathway in fibrosis (59-62).

2. β-Adrenergic Receptor-Hippo-Galectin-3 Pathway: Galectin-3, known for its role in various diseases, including cancer and fibrosis, is upregulated through the β-adrenoceptor-AC-cAMP-PKA-Mst1(Hippo) signaling pathway. This pathway enhances inflammation or fibrosis gene expression, resulting in significant collagen accumulation in the heart (63-66).

3. Chronic β-Adrenergic Stimulation: Chronic stimulation of β-adrenergic receptors, especially β2-receptors, has been linked to cardiac fibrosis. This stimulation directly activates fibroblasts, cytokine signaling, and macrophage recruitment, contributing to fibrosis. Moreover, it influences the production of connective tissue growth factor (CTGF) and vascular endothelial growth factor (VEGF) in cardiomyocytes, promoting fibroblast proliferation and collagen synthesis (60, 67, 68).

4. TRP Ion Channels: The TRP ion channel family, including TRPC6, TRPM7, and TRPV4, is implicated in myocardial fibrosis. These channels, particularly TRPM7, are upregulated by ISO treatment and are involved in myofibroblast conversion, a critical step in fibrotic remodeling (60, 69, 70).

5. Key Molecules Influencing Cardiac Fibrosis: Pin1, elevated post-ISO challenge, induces fibrosis via oxidative stress and the activation of MEK1/2-ERK1/2 signaling. PDGF-A and PDGF-C protein levels increase

following ISO exposure, with tyrosine kinase inhibitors like imatinib mesylate attenuating their effects. Additionally, MicroRNA-30e and MicroRNA-135a, downregulated post-ISO, can mitigate myocardial fibrosis by inhibiting specific signaling pathways and ion channels (36, 71).

Conclusion: Cardiac fibrosis resulting from catecholamine-induced cardiotoxicity involves a complex interplay of signaling pathways and molecular mechanisms. Understanding these processes is crucial for developing targeted therapies to mitigate fibrotic changes in the heart associated with conditions like stroke and Tako-tsubo syndrome. This intricate balance of pathways, from TGF-β signaling to the activation of specific receptors and ion channels, underscores the multifaceted nature of cardiac fibrosis in response to catecholamine exposure.

1.3.5. Cardiac hypertrophy

Cardiac hypertrophy, a response to catecholamine exposure such as ISO and NE, has been extensively studied and linked to various cellular and molecular mechanisms (43, 72)

1. G Protein-Coupled Receptors (GPCR) Kinase Mechanism: The pathological hypertrophy arising from chronic β-adrenergic receptor stimulation is regulated by GPCR kinase (GRK)-β-arrestin signaling. GRK2 and GRK5, part of the β-adrenergic receptor kinase and GRK4 subfamilies, are prominent in the heart and play critical roles in hypertrophic gene regulation through mechanisms like histone deacetylase 5 (HDAC5) phosphorylation and NFAT modulation (73).

2. Calcium Signaling: Calcium, as a key second messenger for GPCRs, drives cardiac hypertrophy via the calcineurin-NFAT and CaMKII-myocyte enhancer factor 2 (MEF2) signaling pathways. Calcineurin activates MEF2 and facilitates NFAT nuclear translocation. The interplay between NFAT and nuclear transcription factors enhances gene transcription related to hypertrophy (74, 75).

3. Epac1 and Cardiac Hypertrophy: β-Adrenergic activation increases Epac1 expression, elevating cAMP levels. Epac1 influences pathological hypertrophy via calcineurin–NFAT and CaMKII–MEF2A pathways in a PKA-independent manner and plays a part in HDAC5 nuclear export (73).

4. MAPK Signaling Pathway: MAPK signaling, particularly ERK1/2 activated by ROS, contributes to cardiac hypertrophy. NADPH oxidase is a key player in catecholamine-induced ROS generation. ERK1/2 regulates pro-hypertrophic gene expression and activates GATA4, while ERK5 increases expression of cardiac fetal genes. The p38 and JNK pathways, activated in response to catecholamine stimulation, also participate in this process(73, 74).

In summary, catecholamine-induced cardiac hypertrophy involves a complex interplay of signaling pathways and molecular players, ranging from GPCR kinases and calcium signaling to epigenetic modifications and mitochondrial dynamics. Understanding these pathways offers insights into potential therapeutic targets to mitigate hypertrophy in cardiotoxicity induced by catecholamines. Catecholamine exposure leads to cardiac hypertrophy, mediated by mechanisms such as GPCR kinase signaling, Ca2+ signaling, Epac1, MAPK signaling pathway, and other molecular factors.

The interaction of catecholamine-induced cardiotoxicity with various cellular pathways underscores its complexity. Oxidative stress, calcium signaling, apoptosis, inflammation, fibrosis, and hypertrophy are interconnected processes driving the cardiotoxic effects of catecholamines. Understanding these mechanisms is crucial for developing therapeutic interventions for stroke-heart syndrome and related cardiac conditions. The majority of knowledge in this field comes from animal models and cell studies, highlighting the need for further research to fully understand these processes in human physiology.

1.3.6. Gut dysmicrobiosis

Additional contributing factors involve intricate interactions among intestinal flora, the central nervous system (CNS), and the cardiovascular system. Some studies propose that patients may experience disruption in intestinal permeability following an acute stroke. This post-stroke alteration in intestinal permeability leads to the migration of bacteria and endotoxins into the bloodstream, triggering an increase in pro-inflammatory cytokines and systemic inflammation, which can exacerbate myocardial damage (76). Furthermore, the translocation of bacteria and endotoxins has an impact on blood metabolites, including indoxyl sulphate and trimethylamine-N-oxide. Indoxyl sulphate influences cardiac remodelling through the NFkB pathway (77), while trimethylamine-N-oxide is linked to cardiac dysfunction, heart failure, and an increased propensity for thrombosis (78).
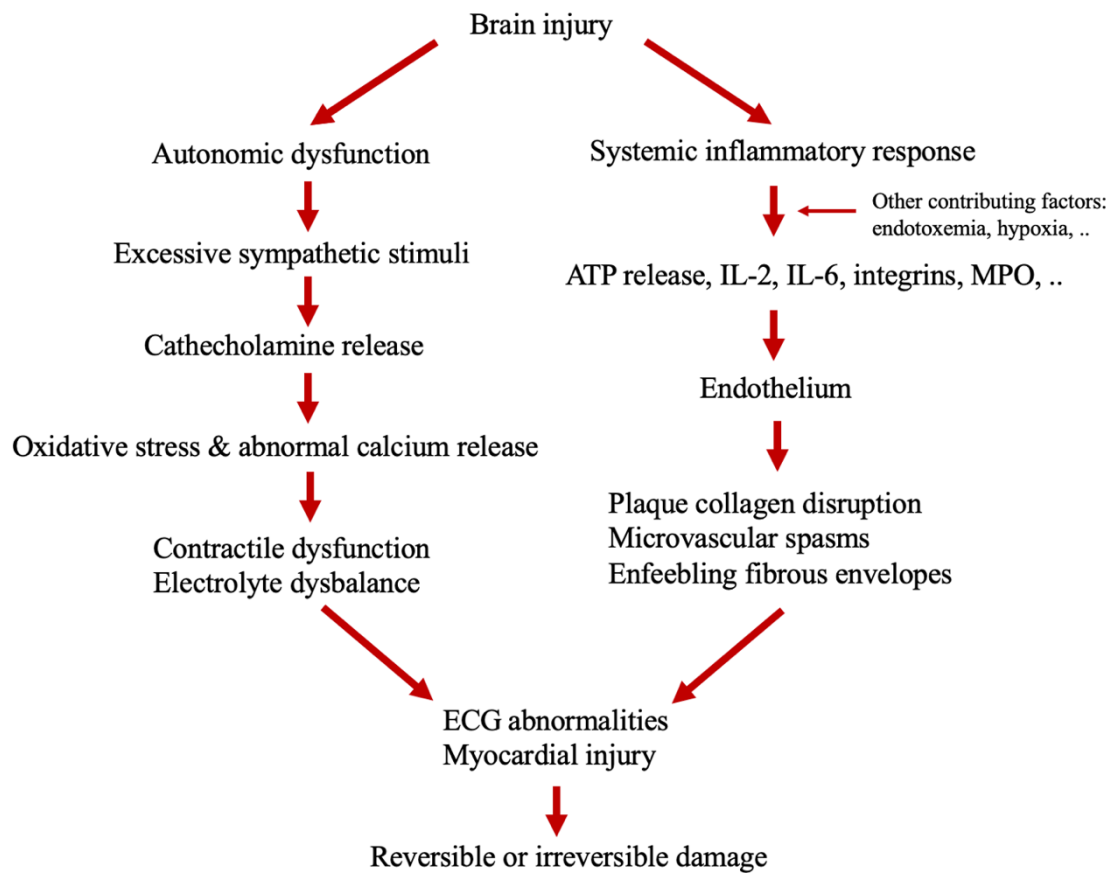

Figure 1. Mechanisms of the cardiac changes after brain injury.

1.4. Specific brain location and cardiovascular system

Substantial evidence underscores the pivotal role of cerebral regions in modulating cardiac function. The engagement of cerebral structures in cardiac activity primarily occurs through the sympathetic and parasympathetic nervous systems, influencing metabolic balance, cardiomyocyte contraction, and heart rate modulation (79). Certain studies have indicated a right-sided dominance in the brain for sympathetic cardiovascular effects. Notably, attention has been directed toward the insula as a key player in regulating cardiac functions (80-82). The insula cortex exerts influence over various autonomic responses, projecting directly to the lateral hypothalamus, parabrachial nucleus, and nucleus of the solitary tract, which, in turn, project directly to sympathetic pre-ganglionic areas. Studies have drawn associations between the insula cortex and cardiac events, revealing a lateralization pattern. Damage to the right insula cortex may heighten sympathetic activity, potentially causing cardiac injury, while left insula cortex damage may elevate parasympathetic activity. Research by Cechetto et al. demonstrated alterations in arterial blood pressure and sympathetic nerve activity induced by specific insula areas. Tokgozoglu et al. found that stroke in the right insula correlated with decreased heart rate variability and an increased incidence of sudden death, suggesting sympathetic dominance after stroke and a potential rise in ventricular arrhythmias. Post-insular stroke, several studies reported ECG abnormalities and increased levels of norepinephrine, brain natriuretic peptide (NT-proBNP), and troponin (cTn) (83-86).

The importance of the insula in autonomic system control and cardiovascular regulation is substantiated by stimulation experiments and human stimulation studies. Oppenheimer et al. demonstrated in rats that micro-stimulation of the insula cortex induces tachycardia or bradycardia, with prolonged stimulation causing heart block, elevated norepinephrine levels, and asystole-induced death. Human studies indicated that stimulating the right anterior insular cortex increases blood pressure and heart rate, while stimulating the left insula results in bradycardia (87, 88). Chouchou et al. reported cardiac dysregulation in nearly half of their study

participants after insular electrical stimulation in epileptic patients, with posterior insula stimulation causing tachycardia and anterior stimulation resulting in bradycardia (89). Nonetheless, comprehensive understanding of insular lateralization and its pathophysiological mechanisms requires further exploration, as only a limited number of studies have delved into isolated insular changes.

1.5. Detecting and Managing Myocardial Changes

Acute stroke is recognized for its potential to induce cardiac abnormalities, encompassing arrhythmias, ventricular dysfunction, myocardial infarction, or even sudden cardiac death. Depending on the underlying pathophysiological mechanisms, stroke can give rise to neurogenic cardiac injury, stemming from disruptions in the autonomic nervous system (ANS) and the release of catecholamines. This may lead to subclinical myocardial injury with elevation in cardiac markers such as troponin and NT-proBNP or could be presented with conditions such as neurogenic stunned myocardium (NSM) and Tako-Tsubo syndrome (TTS) exhibiting similar changes in electrocardiogram (ECG), alterations in cardiac function, and elevated biomarkers similar to myocardial infarction (90).

1.5.1. Troponin and NT-proBNP

Troponins stand out as highly sensitive and specific biomarkers for detecting myocardial injury, demonstrating efficacy in various clinical scenarios. Elevated levels of cardiac troponins (cTn) may be observed in conditions beyond myocardial injury, including acute myocarditis, sepsis, pulmonary embolism, heart failure, and renal insufficiency (91). In the context of acute ischemic stroke (AIS), a study noted an elevation of cTn in 5–8% of patients (92). Fure et al., in their study involving 279 AIS patients, established a significant association between ST

depression and increased levels of highly sensitive troponin T (hs-cTnT). Furthermore, elevated hs-cTnT levels were correlated with a poor short-term outcome in the same study (93). Additionally, the presence of cTn positivity upon admission independently predicts outcome (94). Cardiac enzyme elevation is observed in 10-28% of patients following subarachnoid hemorrhage (SAH) (95, 96). This elevation is linked to increased stroke severity, higher mortality rates, and poorer neurological functional outcomes (97). A retrospective study involving 617 SAH patients also identified elevated mortality in individuals with high levels of highly sensitive troponin I (hs-cTnI) (98). These findings underscore the clinical significance of monitoring troponin levels as a valuable prognostic indicator in both AIS and SAH.

Several studies have reported elevated NT-proBNP following AIS and SAH (7, 86, 99, 100). In some studies, NT-proBNP was elevated in almost two-thirds of patients after AIS, peaking the day after symptom occurrence and declining thereafter (101, 102). Elevated plasma NT-proBNP levels are independently associated with stroke severity, poor functional outcome, and mortality after AIS (103, 104). Montaner et al. showed that B-type natriuretic peptide (BNP) levels are independent predictors of early mortality and neurological worsening after an acute stroke, with no difference between ischemic and hemorrhagic strokes (100). Plasma levels of BNP are independently associated with long-term mortality(105). In the study of almost 600 patients after ischemic stroke, measuring the BNP levels predicted mortality in patients with cardioembolic stroke (106). NT-proBNP is correlated with the NIHSS score and stroke severity and also positively correlated with infarction size and with the modified Rankin Scale (mRS) (86, 100, 107). BNP is elevated in about 75% of cardioembolic strokes. In many cases, the etiology of cardioembolic stroke is embolization from the left atrium, mostly from thrombi that form in atrial fibrillation. The presence of atrial fibrillation is associated with elevated BNP levels, and the BNP level is an independent risk factor for cardioembolic stroke (107, 108). Another study found no significant association between NT-proBNP and infarction size or stroke severity (109).

1.5.2. Other markers of myocardial injury

1.5.2.1. TRAIL

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) belongs to the Tumor necrosis factor ligand superfamily and exists either as a transmembrane protein on the cell surface of various cell types or is released as a soluble protein. It acts as a cell signalling mediator through its receptors TRAIL-R1/DR4 and TRAIL-R2/DR5, initiating caspase activation and programmed cell death across multiple cell types. However, TRAIL also exhibits the ability to bind to decoy receptors TRAIL-R3/DcR1 and R4/DcR2, as well as Osteoprotegerin, contributing to a more intricate system with diverse biological effects (110). TRAIL and its receptors are expressed in different cell types, including endothelial cells, vascular smooth muscle cells, and inflammatory cells (111, 112).

Studies by Kakareko et al. have implicated TRAIL in cardiovascular diseases (113). Lower plasma TRAIL levels have been linked to acute myocardial infarction (AMI) and worse left ventricular ejection fraction in ST-elevation AMI in patient studies (114).   TRAIL has been proposed as a potential predictor of poor prognosis in patients post-AMI, those with coronary artery disease (CAD), or advanced heart failure (115-117). Moreover, studies by Volpato et al. revealed an increased risk of death in patients with prevalent cardiovascular disease and lower TRAIL levels compared to those with higher values, with elevated all-cause and cardiovascular mortality associated with the lowest TRAIL levels (115, 118). In acute stroke, TRAIL levels were significantly lower compared to the standard population (119).

In our study we aimed to elucidate the dynamic changes in TRAIL levels during the acute phase after stroke. The focus is on understanding its association with stroke severity, its impact on short-term outcomes, and its prevalence in cardiovascular involvement. We assessed TRAIL levels in one hundred and twenty patients (63 men, 57 women) of mean age 70,9 ± 13,2 years,

104 with acute ischemic stroke (AIS), we also enrolled 16 patients with intracerebral haemorrhage (ICH) for comparison. In AIS group 73% of patients received reperfusion therapy (29 patients underwent mechanical thrombectomy, 69 patients received intravenous thrombolysis). The cut-off value for lower plasma TRAIL levels was set as 64 pg/ml, the level was defined from the median TRAIL level in our patients and published studies as compared with the control group (120).

1.5.2.2. GDF-15

GDF-15 is emerging as a biomarker of cardiometabolic risk and disease burden. Growth differentiation factor 15 (GDF-15) belongs to the transforming growth factor-ß superfamily and is recognized as a distinct member. Naturally, it is present in minimal concentrations across various organs, encompassing the liver, kidneys, heart, and lungs (121). While the precise function of GDF-15 in the body remains incompletely understood, its primary role is likely associated with metabolic regulation (122). It is implicated in essential regulatory functions associated with inflammation, as well as pro- and anti-apoptotic processes within damaged and diseased tissues. In the presence of inflammation, there is a notable increase in the expression levels of GDF-15 (123). In a healthy adult population, the median values of GDF-15 concentrations in plasma are 762 ng/l (25th–75th percentile, 600–959 ng/l) (124). Physiologically, higher concentrations of GDF-15 are observed in advanced age and during pregnancy, particularly when produced by the placenta. Additionally, elevated levels of GDF-15 have been identified in macrophages within atherosclerotic plaques (125). A recent epidemiological study has further established a close correlation between circulating GDF-15 levels and endothelial dysfunction, as well as the burden of atherosclerotic plaques, even after adjusting for traditional cardiovascular risk factors (126-128). Beyond the well-documented elevation of GDF-15 levels in individuals with cancer, renal insufficiency, diabetes, or sepsis, heightened GDF-15 values are also associated with myocardial remodeling (124, 129). Individuals with stable ischemic heart disease, acute coronary syndromes, heart failure (HF) (129), or atrial fibrillation

(AF) (130) exhibit elevated serum concentrations of GDF-15. In these conditions, GDF-15 levels escalate in correlation with the severity of cardiovascular disease (129). Considering this observation, the utilization of GDF-15 as a prognostic biomarker is recommended, substantiated by diverse data. GDF-15 levels emerge as a promising indicator of adverse cardiovascular developments, demonstrating independence from traditional risk factors. This independence extends to established biomarkers such as cardiac troponin, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and high-sensitivity C-reactive protein (hsCRP).

1.5.2.3.   Copeptin

The body's response to stress in the aftermath of an acute cerebrovascular incident involves triggering the hypothalamic–pituitary–adrenal (HPA) axis. Among the earliest physiological reactions to cerebral ischemia, this leads to a hormonal cascade releasing various stress mediators, including arginine vasopressin (AVP) and copeptin. AVP plays a crucial role in regulating water balance in brain tissue and is produced shortly after a stroke, in equimolar amounts to copeptin. However, assessing circulating AVP levels proves challenging due to its instability and rapid clearance from plasma. First described by Holwerda in 1972, Copeptin is a 39-amino acid peptide with a leucine-rich core segment (131). It is glycosylated and shares a precursor peptide with AVP, known as pre-provasopressin, which spans 164 amino acids and includes a signal peptide, AVP, neurophysin II, and copeptin (132). As the C-terminal part of pro-AVP (CT-proAVP), copeptin is co-released with AVP during precursor processing. Unlike AVP, copeptin demonstrates remarkable stability in serum or plasma at room temperature, facilitating its easy and robust measurement(133, 134). It serves as a reliable surrogate marker for AVP, reflecting the activation of the endogenous stress system and showing promise in prognosticating outcomes for stroke patients (134-136). Although the physiological role of copeptin remains elusive, significant knowledge has been amassed regarding the actions of AVP. Upon its release into the bloodstream, AVP exerts peripheral effects by interacting with tissue-specific

G-protein-coupled receptors (GPCRs). Among the predominant receptors are the V1 receptor, which facilitates arteriolar vasoconstriction, and the V2 receptor, responsible for the antidiuretic action in the kidneys. V1 receptors exhibit high density on vascular smooth muscle cells, triggering vasoconstriction through an increase in intracellular calcium via G-protein-induced inositol triphosphate and diacylglycerol pathways (137, 138). In healthy volunteers, copeptin levels typically range from 1 to 12 pmol/L (upper 97.5th percentile), with median values below 5 pmol/L. Men tend to exhibit slightly higher concentrations compared to women, with a median difference of approximately 1 pmol/L. Unlike many other biomarkers, copeptin plasma levels remain consistent across different age groups and show no correlation with age. Copeptin demonstrates a response to changes in plasma osmolality, exhibiting a kinetic increase/decrease pattern similar to AVP (138-140). While the normal copeptin range reflects physiological AVP secretion required to maintain plasma osmolality, in severe conditions such as shock, sepsis, stroke, or cardiovascular diseases, the non-osmotic release of AVP is indicated by a notable surge in plasma copeptin levels, which carries diagnostic and prognostic significance.

Because Copeptin levels are positively linked to the severity of illness and eventual outcome, it has been suggested as a prognostic indicator in acute conditions. Apart from its documented connection with cardiac disease, copeptin appears to hold significance in various realms within cardiovascular health. A recent study highlighted elevated copeptin levels in individuals suffering from ischemic stroke. It's worth mentioning that copeptin appears to effectively reflect the severity of a stroke and distinguish between patients with positive versus negative outcomes. Notably, evaluating plasma copeptin levels could augment the prognostic accuracy of established clinical scoring systems by autonomously predicting both functional recovery and mortality following a stroke. Specifically, heightened copeptin levels upon admission correlate significantly with unfavorable outcomes and increase the risk of all-cause mortality among stroke patients (141-144).

1.5.3. ECG changes

Electrocardiographic alterations manifest in a considerable percentage of patients post-acute ischemic stroke (AIS), ranging from 50% to 80%. Among the most prevalent changes are T wave inversion (15~35%), ST depression (25~33%), and a prolonged QT interval (20~35%). Common arrhythmias observed include atrial fibrillation (15–38%), ectopic beats (30%), sinus tachycardia (24%), and atrioventricular block (21%) (7, 145). Atrial fibrillation, specifically, poses a risk for secondary complications such as ventricular tachycardia, heart failure, or cardiac death. Independent risk predictors for outcomes at three months post-stroke, assessed by the modified Rankin Scale (mRS), encompass atrial fibrillation, atrioventricular block, ST-depression, ST-elevation, and inverted T waves (7, 146). Research by Stead et al. discovered a prolonged QTc interval in 36% of 345 AIS patients at admission, with this prolonged interval significantly linked to decreased survival after three months and worse neurological outcomes (147). Elevated norepinephrine levels were notably associated with QTc prolongation (148). Furthermore, a study involving 625 patients post-ischemic stroke identified an upright T wave in aVR, observed in 32.2% of patients at admission, as a significant independent predictor of death or ischemic stroke recurrence (149). Associations were also established between ST depression and Q waves and increased troponin T levels (93). These findings underscore the intricate relationship between electrocardiographic changes and adverse outcomes in individuals following ischemic stroke.

1.5.4. Echocardiography

Transthoracic echocardiography (TTE) and left ventricular ejection fraction (LVEF) offers valuable prognostic insights into future cardiovascular disease (CVD) risk among AIS patients, yet a systematic assessment of multiple TTE parameters remains limited. The role of echocardiography in patients after AIS has garnered increasing attention due to its ability to assess cardiac structure and

function, identify potential cardiac sources of embolism (CSE), predict outcomes, and guide therapeutic interventions (150, 151).

Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) serve as fundamental tools in the diagnostic workup of patients after AIS. TTE allows for the assessment of cardiac chambers, valves, and systolic/diastolic function, aiding in the detection of CSE such as atrial fibrillation (AF), patent foramen ovale (PFO), intracardiac thrombi, and cardiac tumors. TEE offers superior visualization of intracardiac structures and is particularly useful in detecting complex CSE, evaluating aortic arch atheroma, and guiding therapeutic interventions such as PFO closure (151-153).

Despite routine reporting of LVEF in patients with acute ischemic cerebrovascular disease during hospitalization, its impact on clinical outcomes remains underexplored. Prior studies have focused on specific ranges of LVEF, yielding conflicting results regarding its association with outcomes such as functional disability and stroke recurrence. Findings revealed that in patients with acute ischemic cerebrovascular disease and LVEF ≤60%, lower LVEF levels independently predicted a higher one-year risk of all-cause mortality, with the risk escalating with decreasing LVEF levels. Even within the generally accepted normal range of 50% to 60% for LVEF, there was an increased risk of mortality. Hence, there is a pressing need for comprehensive evaluation of cardiac function post-acute ischemic stroke (AIS) (154, 155). Echocardiography-derived parameters have prognostic implications in patients post-AIS. Reduced left ventricular ejection fraction (LVEF), diastolic dysfunction, left atrial enlargement, and the presence of cardiac thrombi are predictive of adverse cardiovascular events and recurrent strokes. Serial echocardiographic assessments enable risk stratification, inform therapeutic decision-making, and monitor therapeutic efficacy, thereby guiding rehabilitation protocols and long-term management strategies (154-156).

Echocardiography findings influence therapeutic strategies in patients after AIS. Detection of AF prompts initiation of oral anticoagulation to prevent stroke recurrence. Assessment of intracardiac thrombi guides anticoagulant therapy and may necessitate urgent intervention. Evaluation of PFO size and shunt severity

informs the decision for percutaneous closure to reduce the risk of paradoxical embolism. Furthermore, echocardiography-guided therapeutic interventions optimize patient outcomes and reduce the burden of recurrent cardiovascular events (153). Despite its utility, echocardiography in patients following AIS poses certain challenges, including accessibility, technical expertise, and variability in interpretation. Future directions include the integration of advanced echocardiographic techniques such as strain imaging, three-dimensional echocardiography, and contrast-enhanced imaging to enhance diagnostic accuracy and prognostic value. Additionally, collaborative efforts between neurology and cardiology specialties are essential for optimizing the utilization of echocardiography in the post-AIS setting. Integration of echocardiography into routine post-stroke care facilitates personalized management strategies aimed at optimizing patient outcomes and reducing the burden of recurrent cardiovascular events. Continued research and advancements in echocardiography hold promise for further improving patient care in this population.

1.5.5. Distinguishing myocardial injury

Distinguishing between myocardial injury resulting from neurological alterations, myocardial infarction or isolated ECG abnormalities can be challenging (Tab. 1). Consequently, neurologists must carefully assess the patient's history of ischemic heart disease and chest pain, especially when sudden circulatory deterioration occurs. Indicators of myocardial infarction include dynamic changes in ST segments, new Q waves, new bundle branch block, or malignant ventricular arrhythmia. The elevation and subsequent decline in troponin levels also suggest myocardial infarction (157, 158). While coronary angiography is warranted when the diagnosis of acute myocardial infarction is nearly certain and poses a greater risk to the patient than the ongoing stroke, caution is necessary due to the potential for haemorrhagic transformation when administering heparin during the procedure.

Although many stroke patients may not experience myocardial infarction, the emergence of new ECG changes and elevated biomarkers can indicate myocardial injury and heightened cardiovascular risk. It is crucial not to overlook these patients, and they should undergo a comprehensive cardiac examination, including early echocardiographic assessments to exclude wall motion abnormalities. Patients showing abnormalities during hospitalization should be considered for long-term cardiology follow-up, ambulatory ECG monitoring, and regular echocardiography. Moreover, high-risk individuals with biomarker, ECG, and echocardiographic changes may warrant further investigations such as CT coronary angiogram, cardiac magnetic resonance imaging, or coronary angiography to rule out ischemic heart disease (Fig. 2).

	Indicates a myocardial infarction	Signs against myocardial infarction
Anamnesis	chest pain ischemic heart disease symptoms of acute heart failure	no symptoms no ischemic heart disease
ECG changes	ST segment elevation/depression new pathological Q waves new LBBB, RBBB or AV block malignant arrhythmia	no signs of acute changes
Troponin	sudden high elevation with subsequent fall of levels of troponin	negative or stationary elevation
Echocardiography	new regional wall motion abnormality	no abnormality
Coronarography	acute closure or critical stenosis	without significant stenosis

Table 1. Diagnosing patients for myocardial infarction with acute stroke
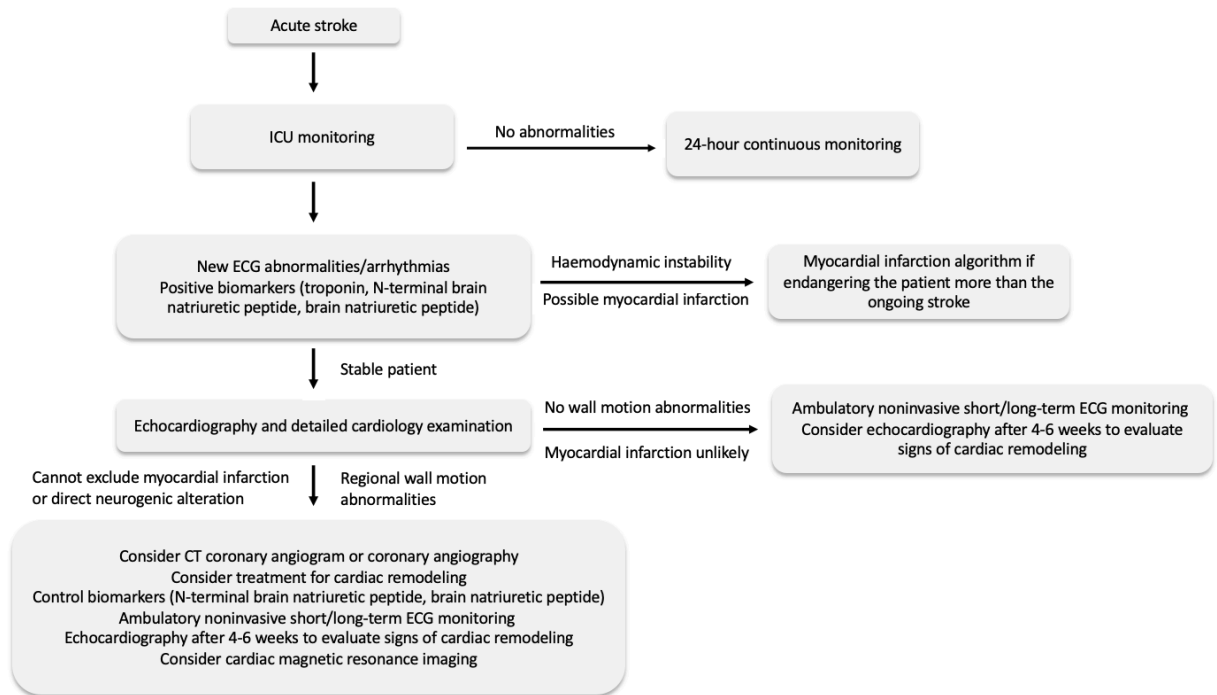
Figure 2. Steps for detecting and managing cardiac complications after acute stroke.

2. Hypothesis and aim of work

Hypothesis:

Acute stroke can cause myocardial injury that is associated with worse patients outcome.

Aims:

1. Analyse dynamic changes of specific biochemical markers of myocardial injury and their effect on outcome.

2. Evaluate subclinical electrocardiographic and echocardiographic changes, prevalence and impact on outcome.

3. Population and methodology

3.1. Study design and patients

The study population consisted of consecutive patients after AIS who were admitted in the Department of Neurology, University Hospital Kralovske Vinohrady, Prague between August 2020 and August 2022. Inclusion criteria were AIS diagnosed on clinical and non-contrast head CT results, supplemented by CT angiography or magnetic resonance. All available clinical data and other predictor variables (demographics, hemodynamics, and blood results) were obtained. Demographic features and clinical information were collected and included age, gender, smoking, previous stroke, or transient ischemic attack (TIA), hypertension, diabetes mellitus, renal impairment (plasma creatinine > 134 mmol/L) and cardiac diseases (coronary artery disease, heart failure and atrial fibrillation). Standard neurologic examination was performed, stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) at the time of admission, defined with the scale: no stroke symptoms (0), minor (1–4), moderate (5–15), moderate to severe (16–20), and severe (21–42). Functional outcome was evaluated using the modified Rankin Scale (mRS) including death within the first 90 days, defined as the categories: no symptoms (0), no disability despite symptoms (1), slight disability (2), moderate (3), moderate to severe (4), severe (5), and death (6).

In our study, according to the fourth universal definition of myocardial infarction (MI), we divided patients after AIS into 3 groups: "no injury" - defined as negative hs-cTnI, "acute injury" – defined by elevated hs-cTnI values above the 99th percentile upper reference limit (URL) and occurrence of the rise and/or fall of cardiac troponin values >20% and "chronic injury" defined by elevated hs-cTnI above URL, but without subsequent change >20%. Cut off in our hospital for hs-cTnI elevation is 53 ng/l for men and 34 ng/ml for women. Exclusion criteria at admission included history of acute myocardial infarction, severe valve disease, heart failure with reduced ejection fraction, patients less than 18 years. The study

was approved by the local Ethics Committee, and written informed content was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

3.2.   Laboratory analysis

Venous blood samples were obtained from patients within the first 48 hours: at the time of admission, 24 ± 12 and 48 ± 12 hours later. Analysis for plasmatic levels of hs-cTnI, NT-proBNP, Copeptin, TRAIL, and GDF-15 was performed at these time points. Collected blood was separated by centrifugation of the blood (3500 rpm, 15 min) and afterward stored at -70°C before analysis. Serum levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN), following the manufacturer's instructions and analysed with an ELISA reader. Moreover, haematology (e.g., haemoglobin level, leukocyte count, and platelet count) and standard biochemistry analysis including potassium, creatinine and CRP levels were obtained at the same timeframe.

3.3.   Electrocardiogram and Echocardiography

Twelve-lead ECGs were obtained at the time of admission, 24 ± 12 hours later, 48 ± 12 hours later, and at the discharge of the patients by the nurses. The ECGs were analysed by one cardiologist who was blinded to all clinical data. The following changes were recorded when abnormal: atrial fibrillation (AF), atrial flutter, sinus tachycardia: HR > 100/min, sinus bradycardia: HR < 60/min, atrioventricular block, first-, second-, and third-degree, ventricular tachycardia (more than three beats of ventricular origin), ectopic ventricular beats, ST-elevation, ST-depression, isoform T-wave, inverted T-wave, U-wave, and QTc > 0.45s for men and >0.46s for women. Standard echocardiographic examination was performed within the first 7 days of hospitalization if patients were eligible to

determine left ventricular function and regional wall motion abnormality, moreover global longitudinal strain was assessed if the image quality was sufficient.

3.4. Statistical analysis

According to our aims following endpoints were assessed – elevation or decrease in biochemical markers, ECG changes, myocardial injury defined according to fourth universal definition of myocardial infarction (MI). Categorical variables were documented as frequencies or counts, expressed as percentages. The distribution of continuous data was assessed using the Kolmogorov-Smirnov test. Continuous variables were presented in graphs and tables as the mean and standard deviation if they followed a normal distribution. Parameters deviating from normality were subjected to analysis using the Mann-Whitney U test or the Kruskal-Wallis test, and the results were conveyed as the median. For continuous variables exhibiting a normal distribution, Student's t-test was employed, and the findings were described as the mean ± standard deviation. To discern differences between categorical variables, a chi-square test or Fisher's exact test was applied. Statistical significance was determined at a level of $p < 0.05$. Survival analyses were estimated by the Kaplan-Meier method and compared by the log-rank test. Statistical analyses were performed primarily in IBM SPSS Statistics version 26.

4. Results

4.1. Dynamic changes of specific biochemical markers of myocardial injury and their effect on outcome.

We enrolled a total of 217 patients, with 118 being male. The mean age of the patients was 70.3 ± 12.5 years. Within our cohort, 73% of patients received reperfusion therapy, with 65 undergoing mechanical thrombectomy and 146

receiving intravenous thrombolysis. Common comorbidities included arterial hypertension, dyslipidaemia, type 2 diabetes mellitus, and atrial fibrillation. The majority of patients were admitted within 12 hours of symptom onset. In analysis, biochemical markers were assessed at the time of admission, 24 ± 12 and 48 ± 12hours later. Hs-cTnI was assessed in all 217 consecutive patients, TRAIL was consecutively assessed in 120 patients with afterwards published article. NT-proBNP, GDF-15 and Copeptin were consecutively assessed in 177 patients.

4.1.1. Hs-cTnI

Myocardial injury in patients after acute ischemic stroke

Among the 217 patients, 59 had elevated hs-cTnI levels above the reference values (>53 ng/ml for men, >34 ng/ml for women), accounting for 27.2%. Those with myocardial injury were older (76.4 ± 12.6 vs. 68.2 ± 9.9, P < 0.001). Within our cohort, 158 patients (72,8%) exhibited no myocardial injury, 34 patients (15.7%) presented with acute myocardial injury, and 25 patients (11.5%) displayed chronic myocardial injury during the acute phase following stroke (Fig. 3a). Notably, a higher proportion of female patients, compared to male patients, presented with both acute and chronic injuries (P=0.015) (Fig. 3b). Analysing treatment strategies, 35.4% of patients after mechanical thrombectomy and 28.8% of patients after intravenous thrombolysis exhibited elevated hs-cTnI levels, with no discernible association between treatment strategy (p=0.34) (Fig. 3c). Patients with myocardial injury had a higher prevalence of comorbidities such as diabetes mellitus, coronary artery disease (CAD), atrial fibrillation, and renal insufficiency. In the group without injury, 77.8% presented with minor to moderate stroke (NIHSS 1-15), compared to 61% in patients with injury. Moreover, 14% of patients without injury presented with moderate to severe or severe stroke (NIHSS 16-42), in contrast to 38% in patients with injury (p=0.001).
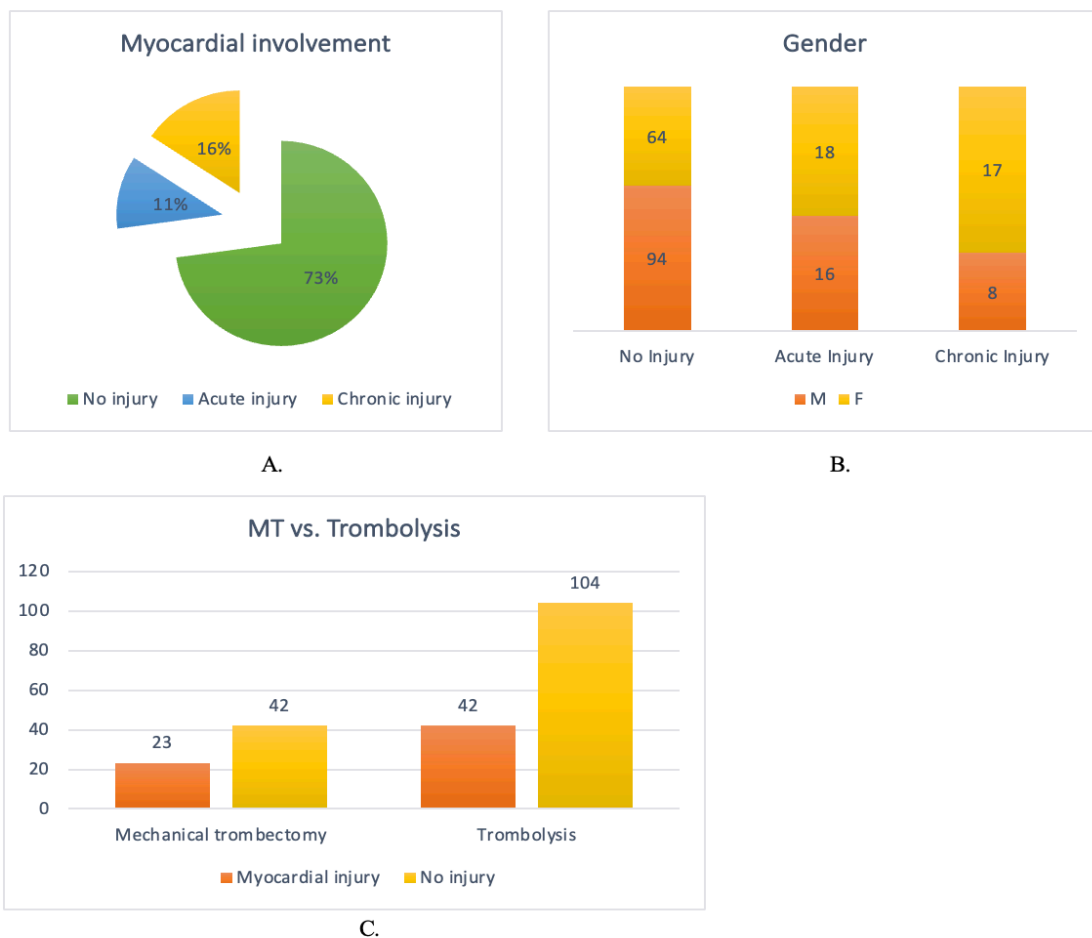
Myocardial involvement

- No injury 73%
- Acute injury 11%
- Chronic injury 16%

A.

Gender

	No Injury	Acute Injury	Chronic Injury
M	94	16	8
F	64	18	17

B.

MT vs. Trombolysis

	Mechanical trombectomy	Trombolysis
Myocardial injury	23	42
No injury	42	104

C.

Figure 3. Myocardial injury in patients after Acute ischemic stroke: (A) prevalence of acute and chronic myocardial injury after AIS; (B) Gender differences; (C) Different treatment strategies and prevalence of myocardial injury in patients after AIS.

Moreover, multivariate regression analysis identified variables independently associated with hs-cTnI elevation in patients with acute ischemic stroke (AIS), as summarized (Tab. 2). Statistically significant variables linked to hs-cTnI elevation included CRP>10mg/ml (P=0.048, OR 2.657, 95% CI 1.009-6.996), type 2 diabetes mellitus (P=0.0025, OR 4.809, 95% CI 1.738-13.308), NIHSS>16 (P=0.013, OR 3.686, 95% CI 1.315-10.335), and age>75 (P=0.02, OR 3.198, 95% CI 1.166-8.773).

Variable	OR 95% CI	P-value
CRP≥10	2.657 (1.009, 6.996)	0.048
Type 2.DM	4.809 (1.738, 13.308)	0.0025
Atrial fibrillation	2.048 (0.758, 5.533)	0.16
CAD	0.875 (0.154, 4.972)	0.88
NIHSS≥16	3.686 (1.315, 10.335)	0.013
Renal insufficiency	0.494 (0.069, 3.513)	0.48
Age≥75	3.198 (1.166, 8.773)	0.02

Table 2. Multivariable regression analysis of variables associated with hs-cTnI elevation. CRP- C-reactive protein (mg/ml), DM-Diabetes mellitus, CAD-coronary artery disease, eGFR-estimated glomerular filtration rate; NIHSS-National Institutes of Health Stroke Scale.

Hs-cTnI is associated with stroke severity, worse outcome and death in AIS.

We conducted an analysis to examine the correlation between acute and chronic injuries and their association with functional disability or mortality. In the univariate analysis, we found that chronic injuries were linked to increased mortality at both 30 days (P = 0.006, OR 4.424, 95% CI 1.542-12.693) and 90 days (P = 0.001, OR 4.514, 95% CI 1.809-11.267). Additionally, acute injuries exhibited a more pronounced association with mortality at both 30 days (P < 0.001, OR 6.5059, 95% CI 2.666-15.87) and 90 days (P < 0.001, OR 4.647, 95% CI 2.029-10.639). Furthermore, patients with elevated hs-cTnI levels demonstrated an increased likelihood of an unfavourable outcome (mRS 90days ≥4) in both chronic (P = 0.004, OR 2.9625, 95% CI 1.4072-6.2366) and acute injuries (P = 0.011, OR 2.4688, 95% CI 1.2318 to 4.9477) at 90 days. Stroke severity was associated with both chronic (P = 0.05, OR 2.3407, 95% CI 1.0112, 5.4182) and acute myocardial injuries (P = 0.02, OR 2.4096, 95% CI 1.1447, 5.0721) (Tab. 3). The Kaplan Meier

survival curve demonstrated a higher all-cause mortality in cases of acute and chronic myocardial injuries (P < 0.001) (Fig. 4).

A.	No injury, n=158	Chronic injury, n=25	Unadjusted OR (95% CI)	P value
Death				
30 days	10	7	4.424 (1.5419, 12.6931)	0.006
90 days	14	10	4.514 (1.8087, 11.2669)	0.001
Unfavourable outcome				
mRS 90days ≥4	49	17	2.963 (1.4072, 6.2366)	0.004
Stroke severity				
NIHSS≥16	27	10	2.341 (1.0112, 5.4182)	0.05

B.	No injury, n=158	Acute injury, n=34	Unadjusted OR (95% CI)	P value
Death				
30 days	10	14	6.506 (2.666, 15.876)	<0.001
90 days	14	14	4.647 (2.029, 10.639)	<0.001
Unfavourable outcome				
mRS 90days ≥4	49	19	2.469 (1.232, 4.948)	0.011
Stroke severity				
NIHSS≥16	27	14	2.409 (1.145, 5.072)	0.02

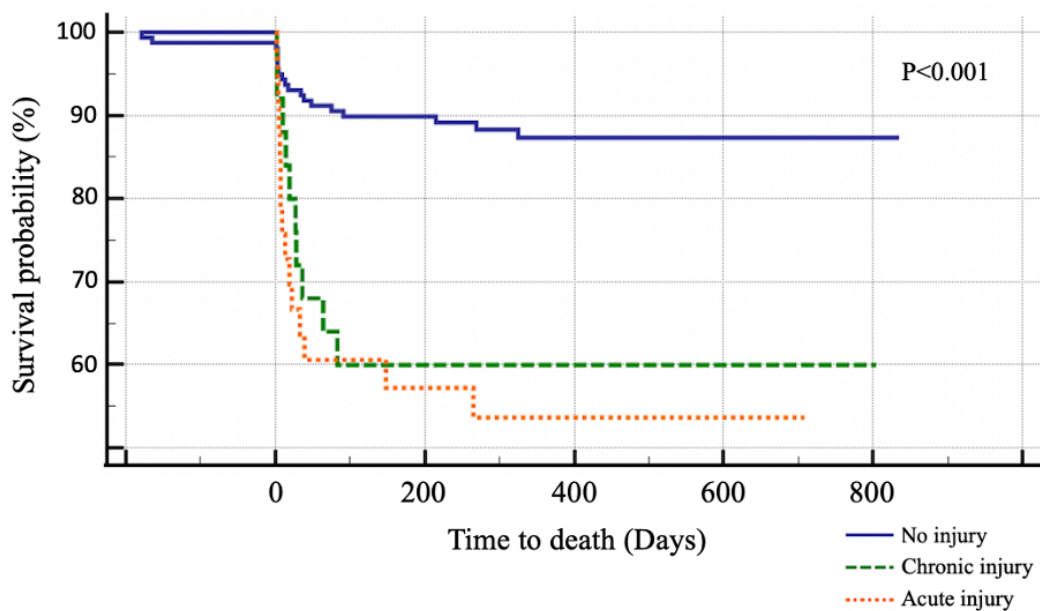**Table 3.** Severity and prognosis in patients with and without myocardial injury

Figure 4. Kaplan-Meier survival curves comparing no injury, chronic injury, and acute injury in patients after acute ischemic stroke.

4.1.2. NT-proBNP

Elevated NT-proBNP predicts worse outcome and mortality in patients after acute ischemic stroke.

To determine levels of NT-proBNP, blood samples were collected from 177 patients upon admission, as well as at 24 and 48 hours thereafter. Of the cohort, 82 patients (46.3%) exhibited elevated NT-proBNP (>125 pg/ml), and 34 patients (19.2%) presented with more pronounced elevation (>450 pg/ml). Common comorbidities in patients with elevated NT-proBNP included arterial hypertension, dyslipidaemia, type 2 diabetes mellitus, and atrial fibrillation. In our analysis, we identified a correlation between elevated NT-proBNP levels and unfavourable outcomes, as assessed by the modified Rankin Scale (mRS) at 90 days ($p < 0.001$), as well as with all-cause mortality at 30 days ($p = 0.001$) and 90 days ($p < 0.001$) (Tab. 4).

The Kaplan-Meier survival curve underscored significantly higher all-cause mortality in patients with elevated NT-proBNP ($p < 0.001$), with no discernible difference between elevations >125 pg/ml and >450 pg/ml ($p = 0.14$). Survival analysis indicated a near-significant association between patients with NT-proBNP >125 pg/ml and a subsequent >20% change in value compared to those with elevated NT-proBNP without a subsequent >20% change (Fig. 5). Additionally, a connection with stroke severity, evaluated by the National Institutes of Health Stroke Scale (NIHSS), was observed ($p = 0.005$) (Tab. 4). The findings suggest that elevated NT-proBNP is linked to stroke severity, unfavourable functional outcomes, and short-term mortality in patients following acute ischemic stroke.
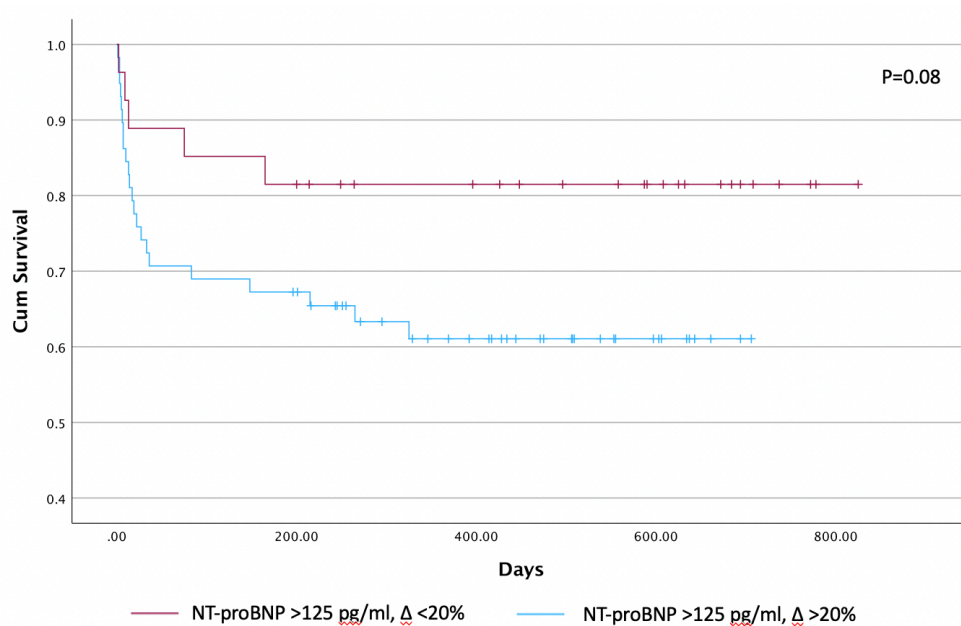
A	NT-proBNP>125pg/ml, n=82	NT-proBNP <125pg/ml, n=95	Unadjusted OR (95% CI)	P value
Death				
30 days	19	5	5.4286 (1.9256 to 15.3038)	0.001
90 days	22	6	5.4389 (2.0820 to 14.2082)	<.001
Unfavourable outcome mRS>3				
90 days	47	22	4.4558 (2.3329 to 8.5106)	<.001
Stroke severity				
NIHSS≥16	27	14	2.8403 (1.3678 to 5.8980)	0.005

B	NT-proBNP Δ >20%, n=58	NT-proBNP Δ <20%, n=24	Unadjusted OR (95% CI)	P value
Death				
30 days	15	4	1.7442 (0.5129 to 5.9310)	0.37
90 days	18	4	2.2500 (0.6715 to 7.5386)	0.19
Unfavourable outcome mRS>3				
90 days	35	12	1.5217(0.5840 to 3.9649)	0.39
Stroke severity				
NIHSS≥16	19	8	0.9744(0.3547 to 2.6764)	0.96

Table 4. Association between elevated levels of NT-proBNP with stroke severity and short-term prognosis in patients after AIS: (A) Elevated NT-proBNP at baseline; (B) Elevated NT-proBNP>125pg/ml at baseline and occurrence of the rise and/or fall of cardiac troponin values >20% vs. elevated NT-proBNP, but without subsequent change >20% .
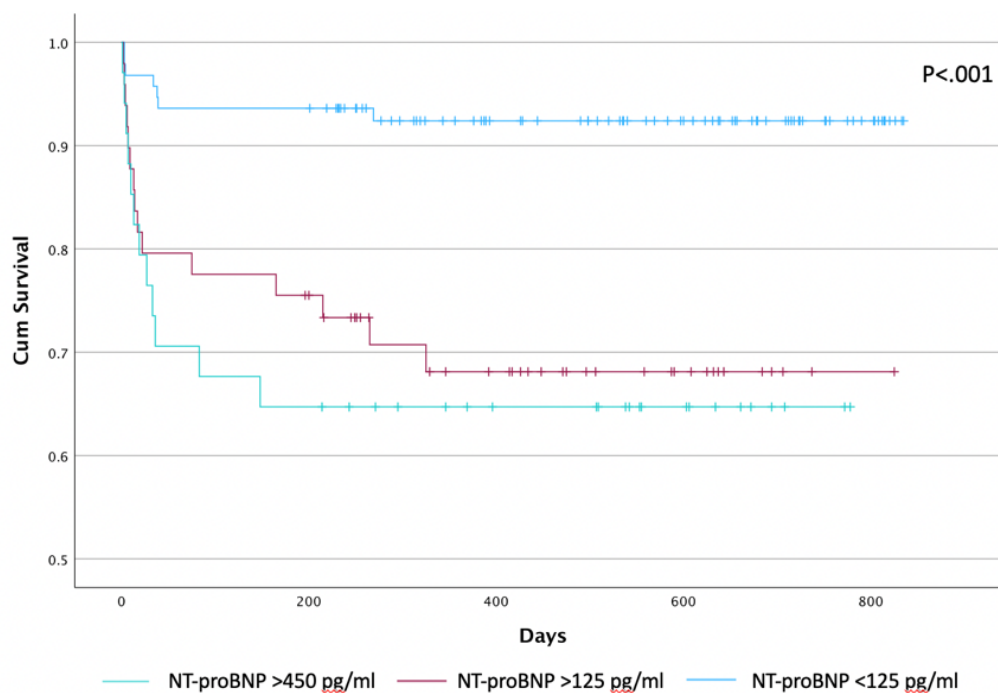
(a)

<p style="text-align:center">(a)</p>

Figure 5. Association between NT-proBNP and all-cause mortality. Kaplan-Meier event rate curves showing cumulative incidence of death according to baseline NT-proBNP (a) and relationship between elevated NT-proBNP>125pg/ml at baseline with occurrence of the rise and/or fall of NT-proBNP values >20% vs. elevated NT-proBNP, but without subsequent change >20% (b).

4.1.3. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)

Characteristics of TRAIL and its dynamic changes after acute stroke

Figure 8 illustrates the TRAIL values at various time points within the initial 48 hours for patients diagnosed with Acute Ischemic Stroke (AIS) and Intracerebral Hemorrhage (ICH). During the first 48 hours of hospitalization, the average TRAIL level was 72.58±32.81 pg/ml for the AIS group and 55.83±30.66 pg/ml for the ICH group.

The mean TRAIL level exhibited a decline within the initial 24 hours of hospitalization, followed by an increase on the second day. Notably, the lowest

TRAIL levels for both groups were observed on day 1, with mean levels of 68.73±33.42 pg/ml for the AIS group and 50.12±27.35 pg/ml for the ICH group. A comparison between the AIS and ICH groups revealed that TRAIL levels were lower in the ICH group, showing significant differences on day 1 (p=0.03) and day 2 (p=0.034) (Fig. 8).
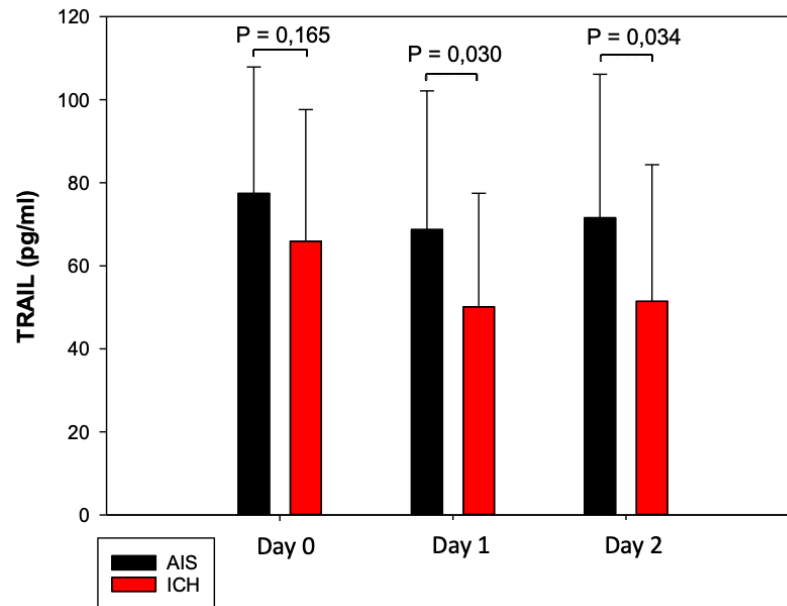

Figure 8. TRAIL levels during first 48 hours of hospitalization in patients after acute ischemic stroke and intracerebral hemorrhage.

TRAIL is associated with stroke severity and worse neurological outcome in AIS

In the context of acute ischemic stroke (AIS), individuals with moderate to severe and severe strokes (NIHSS 16-42) displayed reduced TRAIL levels compared to those with minor to moderate strokes (73.1 pg/ml vs. 51.3 pg/ml, p=0.003) (Fig. 9a). Notably, we identified a correlation between lower TRAIL levels and the presence of moderate to severe and severe strokes (NIHSS 16-42) on day 1 (p=0.044) (Fig. 10c). Examining the 90-day modified Rankin Scale (mRS) score for functional disability, patients facing a more unfavorable outcome or mortality (mRS 90 5-6) exhibited lower TRAIL levels (72.6 pg/ml vs. 43.1 pg/ml, p<0.001) (Fig 9b). This association persisted for severe disability or death on both

day 1 (p<0.0022) and day 2 (p<0.044) (Fig. 10d). Furthermore, a lower TRAIL level on day 1 was linked to mortality at 90 days (p=0.009). In the intracerebral hemorrhage (ICH) group, no significant association was observed between lower TRAIL levels and worse functional outcomes on day 0 (p=0.58), day 1 (p=0.24), and day 2 (p=0.59), although the patient frequency was low. Notably, no significant association was found between lower TRAIL levels and delayed hospital admission beyond 4.5 hours (12.5%, p=0.49), 12 hours (1%, p=0.48), or with wake-up strokes (7.4%, p=0.58).
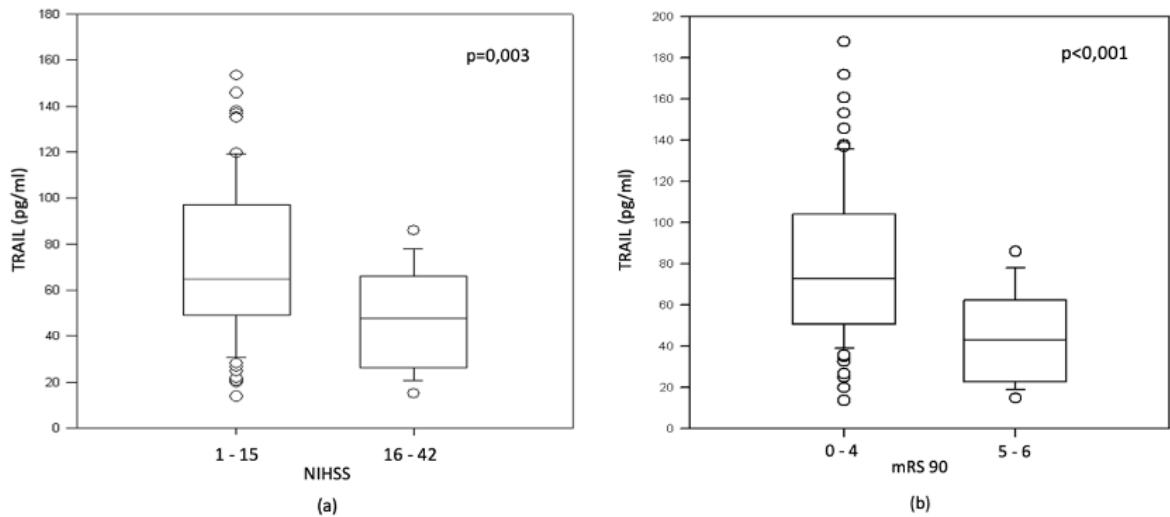

Figure 9. Association between TRAIL levels on day 1 and NIHSS score and mRS at 90 days in patients after AIS. **(a)** Association between TRAIL level and NIHSS score; **(b)** Association between TRAIL level and mRS at 90days;

TRAIL and markers of myocardial injury in patients after acute stroke

In the AIS group, a correlation was identified between lower TRAIL levels and elevated NT-proBNP at admission (p=0.039), after 24 hours (p=0.043), and 48 hours (p=0.023) (Fig. 10a). However, no significant association was found between lower TRAIL levels and elevated hs-cTnI (Fig. 10b). The progression of

cardiac markers and changes in TRAIL levels in the ICH group is illustrated in Figure 11a and 11b.
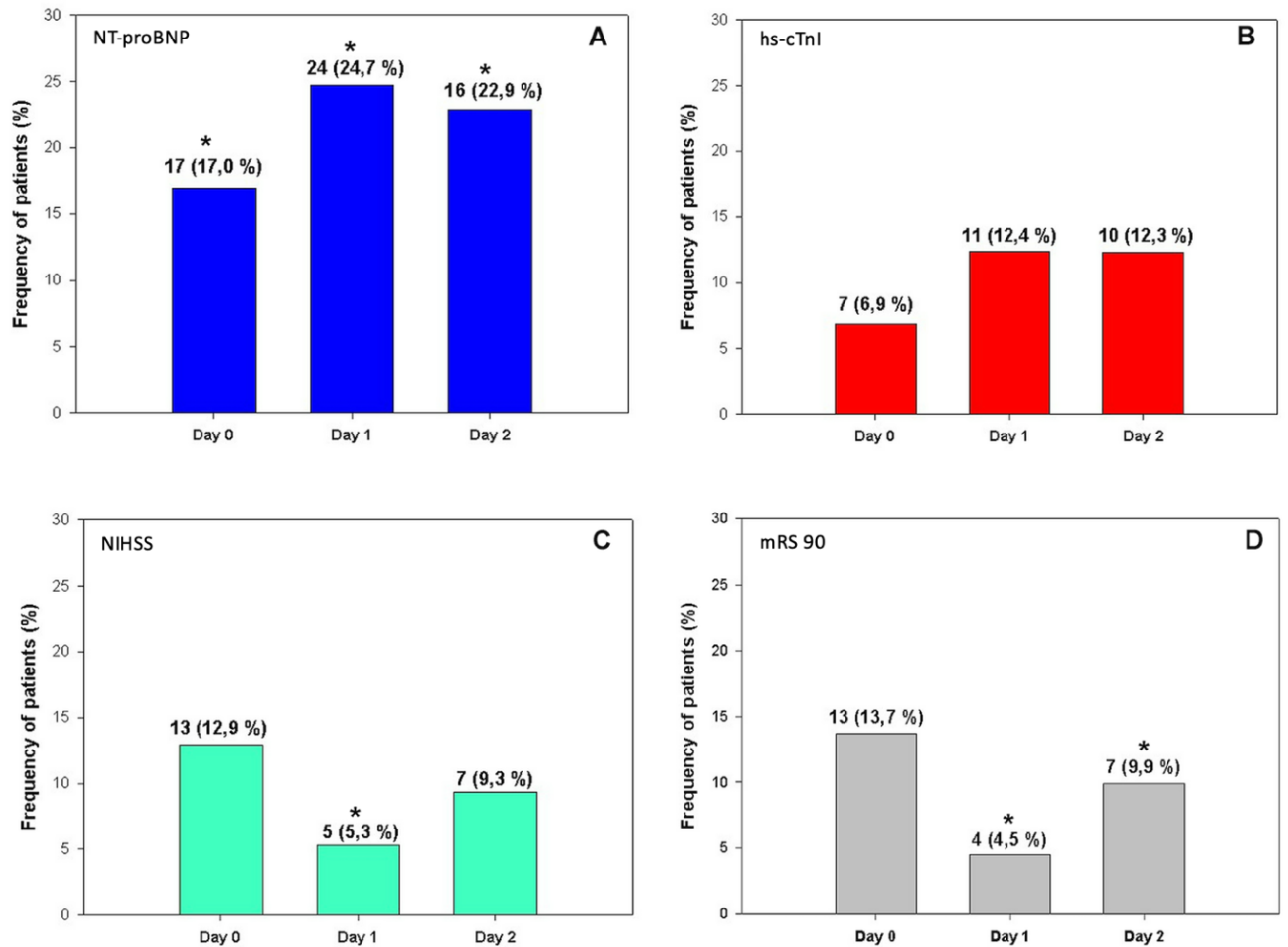

Figure 10. Relationship between lower TRAIL level (<64pg/ml) with markers of myocardial injury, stroke severity and functional outcome in AIS. (a) Lower TRAIL and NT-proBNP elevation >125 pg/ml; (b) Lower TRAIL and hs-cTnI elevation >53pg/ml; (c) Lower TRAIL and moderate to severe stroke (NIHSS 16-42); (d) Lower TRAIL and worse functional outcome or death (mRS at 90 day 5-6). The categorical values are given as frequencies and respective percentages.
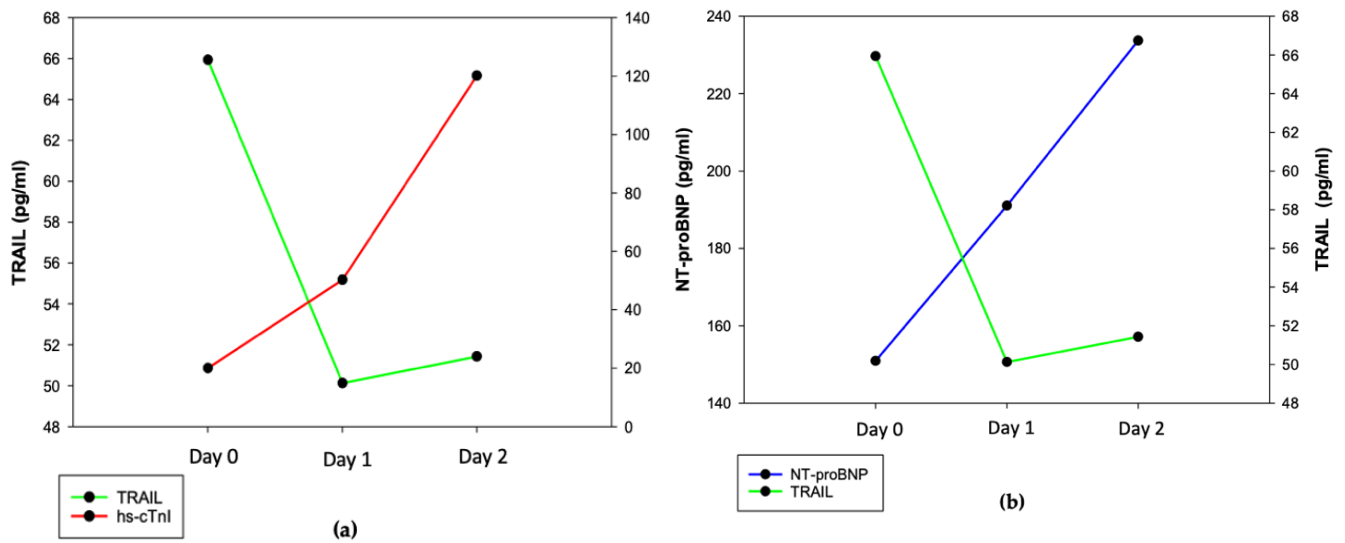
* Represents significant result

Figure 11. Relationship between TRAIL and markers of myocardial injury in patients after ICH. **(a)** Association between NT-proBNP and TRAIL; **(b)** Association between TRAIL and hs-cTnI; Mean values and SD: NT-proBNP day 0: 150,8 ± 143,4, day 1: 191,1 ± 158,9, day 2: 233,7 ± 276,8, TRAIL day 0: 65,9 ± 31,7, day 1: 50,1 ± 27,3, day 2: 51,4 ± 32,9, hs-cTnI day 0: 20,1 ± 23,9, day 1: 50,2 ± 87,8, day 2: 120,1 ± 349,1

4.1.4. GDF-15

GDF-15 is associated with stroke severity, worse neurological outcome and myocardial injury in AIS

Receiver-operating characteristic (ROC) curve analysis was used to determine the diagnostic accuracy and optimal elevation cut-off values of GDF-15 on day 1 for the severity of acute stroke defined by NIHSS score. The optimal cut off in our group was 1776 pg/ml (Sensitivity 0,8, Specificity 0,52).

Between August 2020 and August 2022, 177 patients after AIS were assessed. Elevated GDF-15 was observed in 71 patients (40,1%). In analysis, GDF-15 elevation was associated with myocardial injury (Fig. 12A). Moreover, individuals with moderate to severe and severe strokes (NIHSS 16-42) displayed

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higher GDF-15 levels compared to those with minor to moderate stroke (Fig. 12B) (Tab. 5). Moreover, we observed a connection between elevated GDF-15 with unfavorable functional outcome evaluated by mRS at 90 days (HR 2.568, 95% CI 1,442 to 4,574, p=0.001) (Tab. 5).
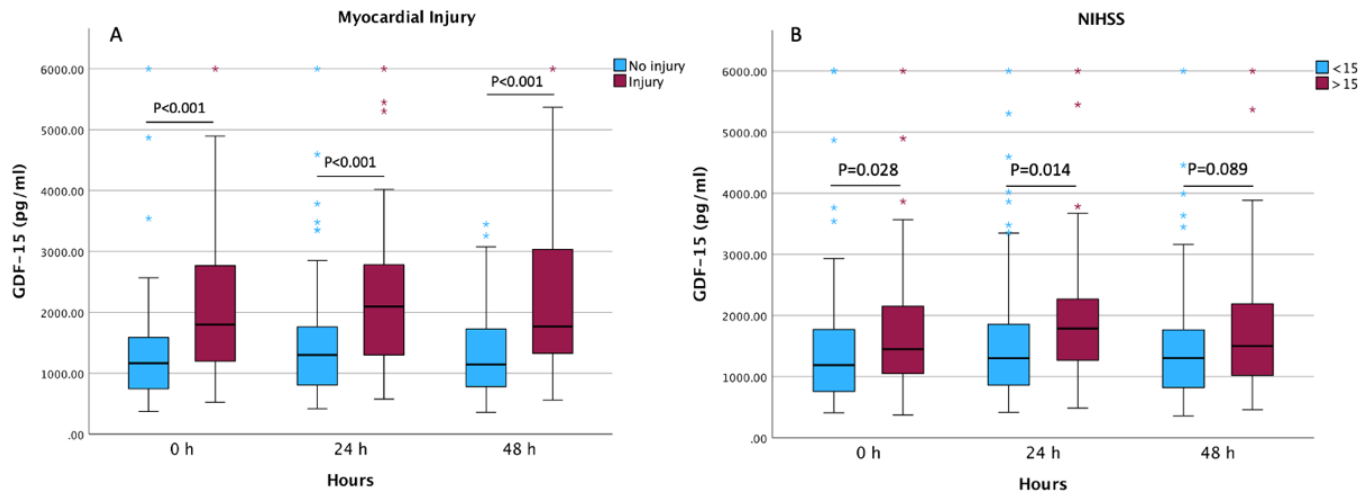
Figure 12. Association between elevated levels of GDF-15 with (A) myocardial injury, (B) NIHSS scale.

n=177	< 1776 pg/ml (n=106)	> 1776 pg/ml (n=71)	Unadjusted OR (95% CI)	P value
Death				
90 days	5	19	5.673 (2.025 to 15.891)	0.001
1 year	7	21	4.479 (1.809 to 11.090)	0.0012
Unfavorable outcome				
mRS 90days ≥4	25	43	2.568 (1.442 to 4.574)	0.0014
Stroke severity				
NIHSS≥16	16	25	2.3327 (1.163 to 4.678)	0.017

Table 5. Association between elevated levels of GDF-15 with stroke severity and short-term prognosis in patients after AIS.

GDF-15 predicts unfavorable clinical outcome in patients after AIS.

We observed a connection between elevated GDF-15 with all-cause death at 90 days and 1 year (Tab. 7). The Kaplan-Meier survival curve accentuated a significantly elevated all-cause mortality among patients with increased GDF-15 (p < 0.001) (Fig. 14). In multivariate regression analysis elevated GDF-15 was associated with atrial fibrillation and high-sensitive troponin I elevation.

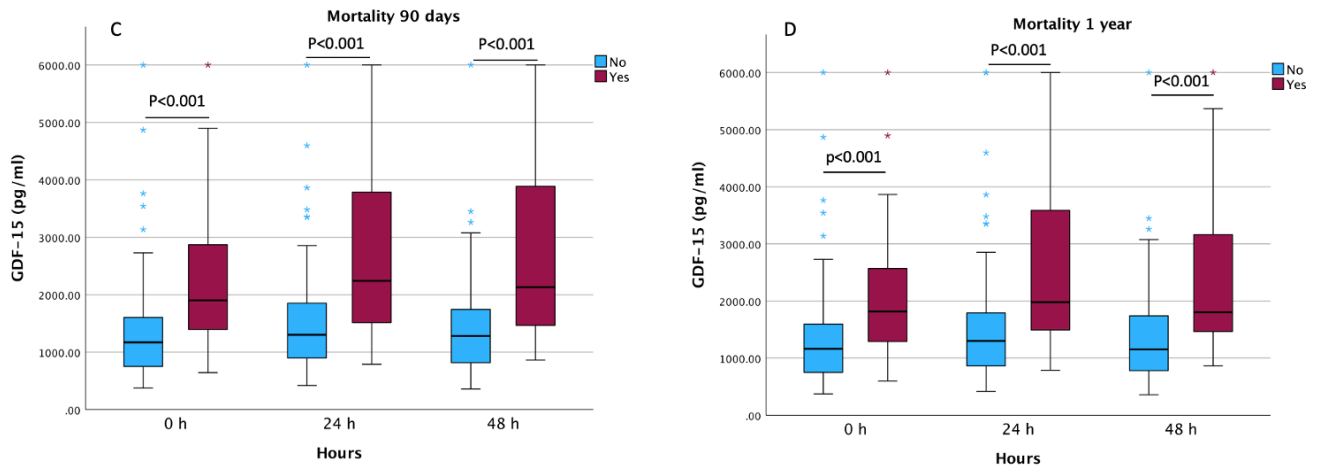

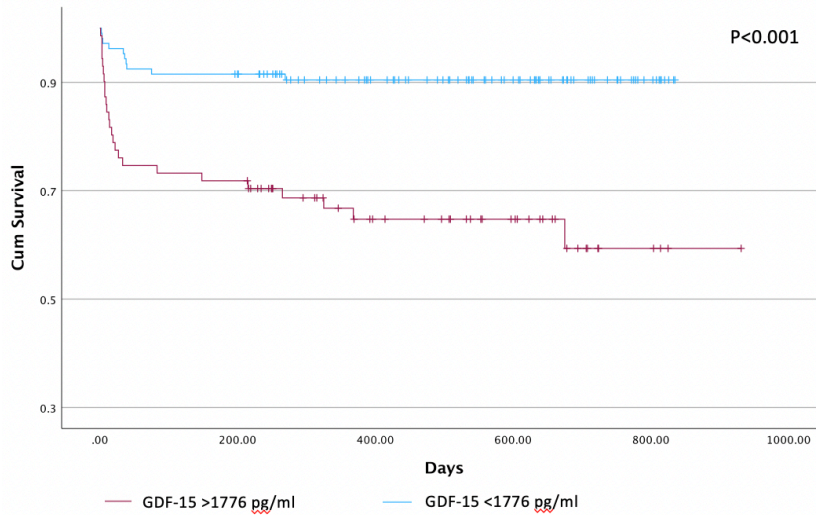**Figure 13.** Association between elevated levels of GDF-15 with 90-day mortality (A), 1 year mortality (B)

Figure 14. Kaplan-Meier event rate curves showing cumulative incidence of death in patients with elevated GDF-15>1776pg/ml

4.1.5. Copeptin

Copeptin predicts unfavorable functional outcome in patients after AIS

We evaluated 177 patients after AIS. Elevated Copeptin was observed in 99 patients (55,9%). In analysis, Copeptin elevation was associated with functional disability evaluated with mRS at 90days on day 1 (Fig. 15A) and with moderate to severe and severe stroke (NIHSS 16-42) (Fig. 15B) at admission and on day 1. However, we did not observe a connection between Copeptin elevation with myocardial injury or year mortality (Fig. 15 C, D). In survival analysis, Kaplan-Meier curve did not confirm association between elevated all-cause mortality among patients with increased Copeptin (Fig. 16).
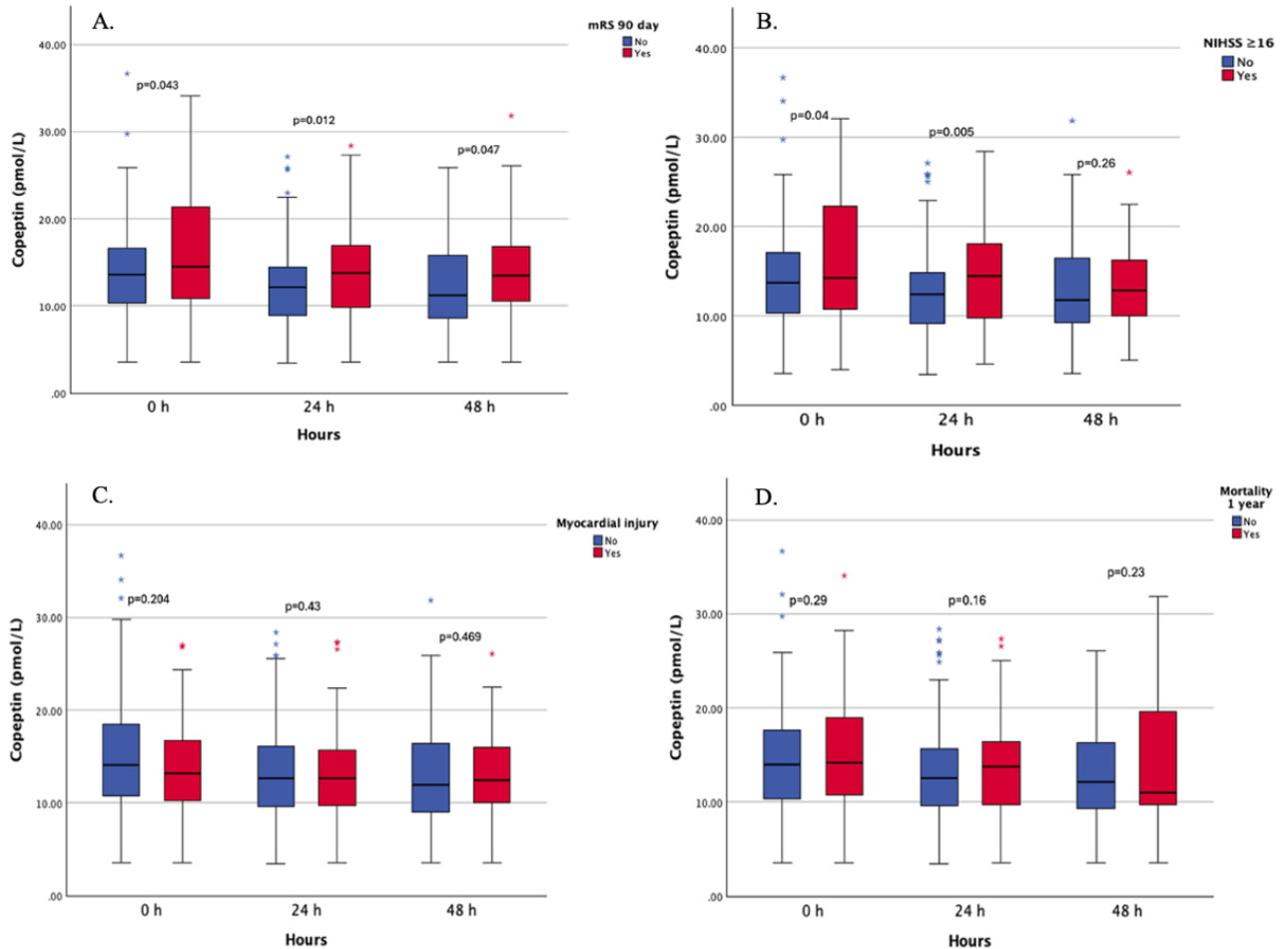

Figure 15. Association between elevated levels of Copeptin with 90-day functional dysability (A), NIHSS scale (B), myocardial injury (C), 1 year mortality (D).
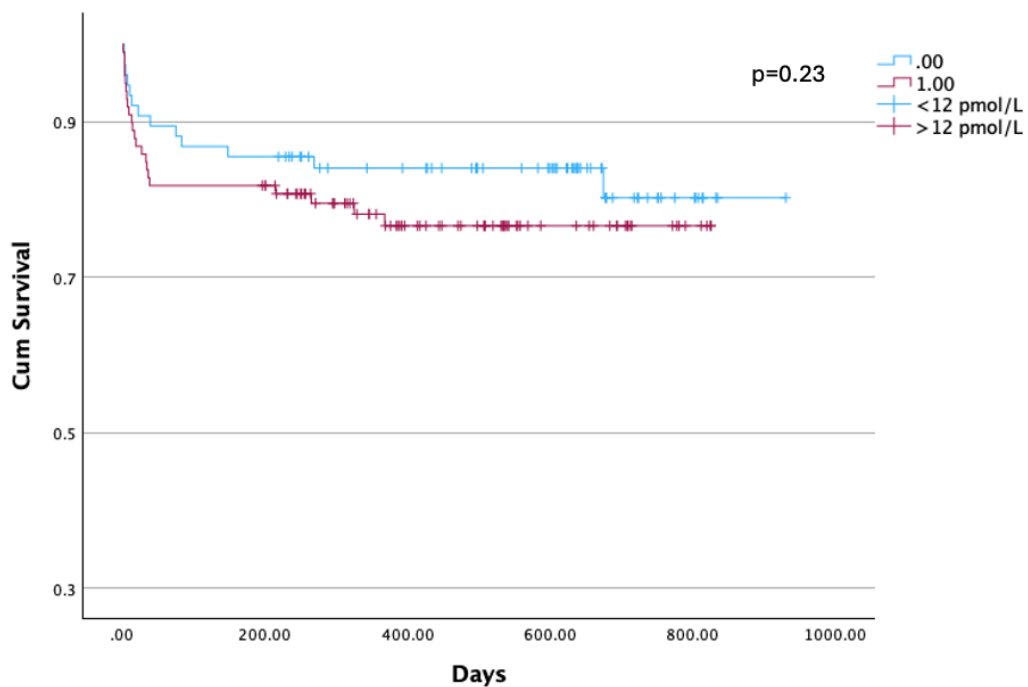
Figure 16. Kaplan-Meier event rate curves showing cumulative incidence of death in patients with elevated Copeptin >12 pmol/L.

4.2. Evaluation of subclinical electrocardiographic and echocardiographic changes, prevalence and impact on outcome.

4.2.1. ECG changes

Within the electrocardiogram (ECG) analysis, we divided patients into 2 groups – "No injury" and "Injury" according to myocardial injury defined by reference values of hs-cTnI. Prevalent ECG alterations comprised T-wave inversion (21.2%), ST depression (15.2%), QTc prolongation (13.4%), and flat T-wave (12%). The relationship between myocardial injury and ECG changes is presented (Tab. 6). Notably, in patients with myocardial injury, there was an elevated incidence of T-wave inversion (P < 0.001, OR 5.535, 95% CI 2.7894-10.981), ST segment depression (P < 0.001, OR 5.356, 95% CI 2.448-11.72), and QTc prolongation (P = 0.001, OR 3.794, 95% CI 1.709-8.42). Atrial fibrillation (AF)

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emerged as the predominant arrhythmia, manifesting in nearly one-third of all patients within the initial 48 hours of hospitalization. Among patients with myocardial injury, AF occurred in 40.6% of cases. However, we did not discern any correlation between myocardial injury and the occurrence of atrial fibrillation. Furthermore, no significant distinctions were observed between acute and chronic myocardial injury.

	No injury, n=158	Injury, n=59	Unadjusted OR (95% CI)	P value
Morphological changes				
T wave inversion	15	31	5.535 (2.7894-10.981)	<0.001
ST segment depression	11	22	5.356 (2.448-11.72)	<0.001
QTc prolongation	12	17	3.794 (1.709-8.42)	0.001
Flat T wave	22	4	0.487 (0.161-1.472)	0.2
U wave	8	7	2.343 (0.813-6.747)	0.11
Hyperacute T wave	3	2	1.785 (0.291-10.953)	0.53
Arrythmias				
Atrial fibrillation	45	24	1.4282 (0.8-2.55)	0.23
AV block I. degree	19	5	0.7047 (0.25-1.97)	0.51
RBBB	12	5	1.11 (0.377-3.303)	0.84
Sinus bradycardia	11	4	0.97 (0.298-3.178)	0.96
LAH	5	5	2.68 (0.758-9.585)	0.13
Sinus tachycardia	4	4	2.678 (0.648-11.055)	0.17

Table 6. Relationship between ECG changes and myocardial injury in AIS. LAH – left anterior hemiblock, RBBB – right bundle branch block

4.2.2. Echocardiography/Global longitudinal strain (GLS) analysis

Two-dimensional speckle tracking echocardiography (2D STE) emerges as a valuable tool, providing detailed insights into myocardial strains and early dysfunction detection, surpassing traditional methods like left ventricular ejection fraction (LVEF) assessment. Studies indicate a strong association between ischemic stroke, heart failure, and adverse outcomes. Post-stroke left ventricular (LV) dysfunction is common, influenced by various factors including neurologic injury, gender, and biomarker levels. Importantly, LV Global Longitudinal Strain (GLS) emerges as a sensitive marker for detecting early myocardial dysfunction, even in patients with preserved LVEF. Research suggests a correlation between stroke severity and LV dysfunction, with even mild impairment detected by 2D STE in the early stages (159, 160).

Global longitudinal strain predicts clinical outcome in patients after acute ischemic stroke without left ventricular dysfunction.

As stated above, global longitudinal strain (GLS) is a sensitive marker of myocardial dysfunction that could help predict risk for future events. In our study, we assessed whether GLS can help predict adverse clinical outcomes in patients after acute ischemic stroke (AIS). Patients without LV dysfunction after AIS were divided into groups according to abnormal GLS (<-15.9%) or normal GLS (>-16%). 155 enrolled patients after AIS had echocardiographic examination, due to image quality or LV impairment, GLS was assessed in 110 patients. In our study, 28 patients (25,6%) had abnormal GLS. After a year follow-up, the overall mortality was more common in patients with abnormal GLS compared to patients with normal GLS (Tab. 7, Fig. 17A). The Kaplan-Meier survival curve accentuated a significantly elevated all-cause mortality among patients with abnormal GLS (Fig 18). Moreover, abnormal GLS was associated with positive hs-cTnI (Fig. 17B), and was connected with unfavorable outcome evaluated by mRS at 90 days (Fig. 17C). At last, severe stroke (NIHSS >15) was not significantly associated with abnormal

GLS (HR 2.2121, 95% CI 0.7091 to 6.9009, p = 0.1714) (Tab. 7). In conclusion in patients after AIS, abnormal GLS could be helpful predictor for clinical events and subclinical myocardial injury.
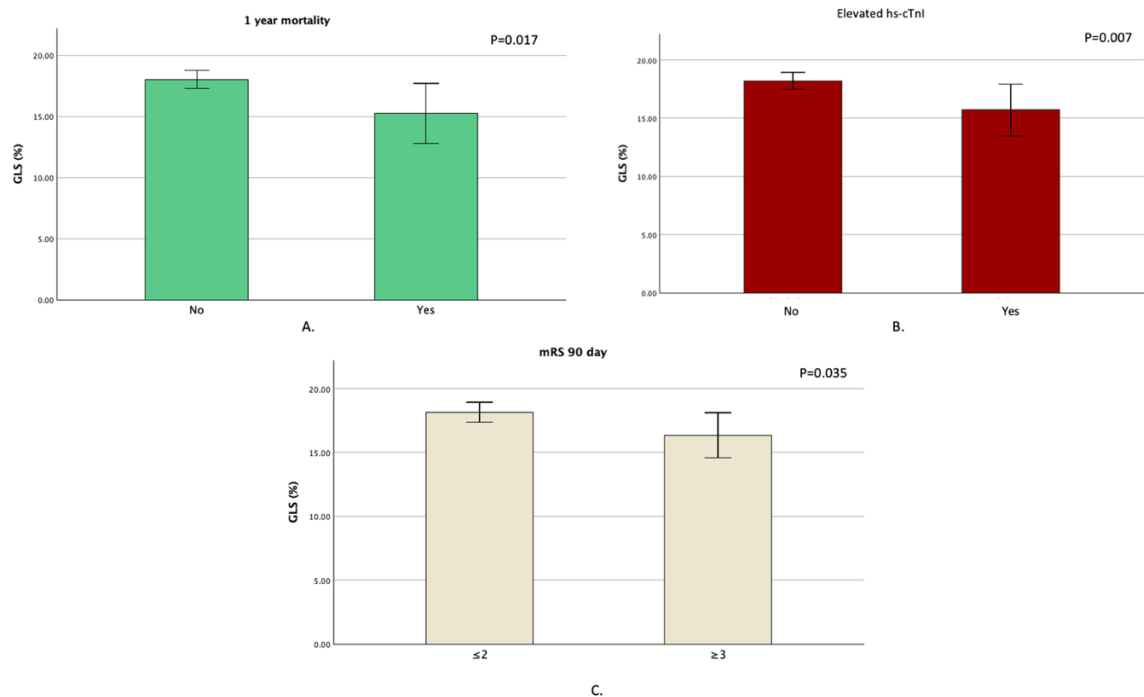
Figure 17. Association between abnormal GLS with 1 year mortality (A), hs-cTnI elevation (B), mRS 90 days (C) in patients after acute ischemic stroke.

n=110	GLS≤15,8 % (n=28)	GLS ≥ 15,9 % (n=82)	Unadjusted OR (95% CI)	P value
Death				
90 days	3	2	6.67 (1.1497 to 38.6581)	0.034
1 year	6	6	3.45 (1.0127 to 11.7842)	0.048
Unfavorable outcome				
mRS 90days ≥4	11	15	2.89 (1.1260 to 7.4187)	0.027
Stroke severity				
NIHSS≥16	6	9	2.21 (0.7091 to 6.9009)	0.171

Table 7. Association between lower GLS with stroke severity and short-term prognosis in patients after AIS.
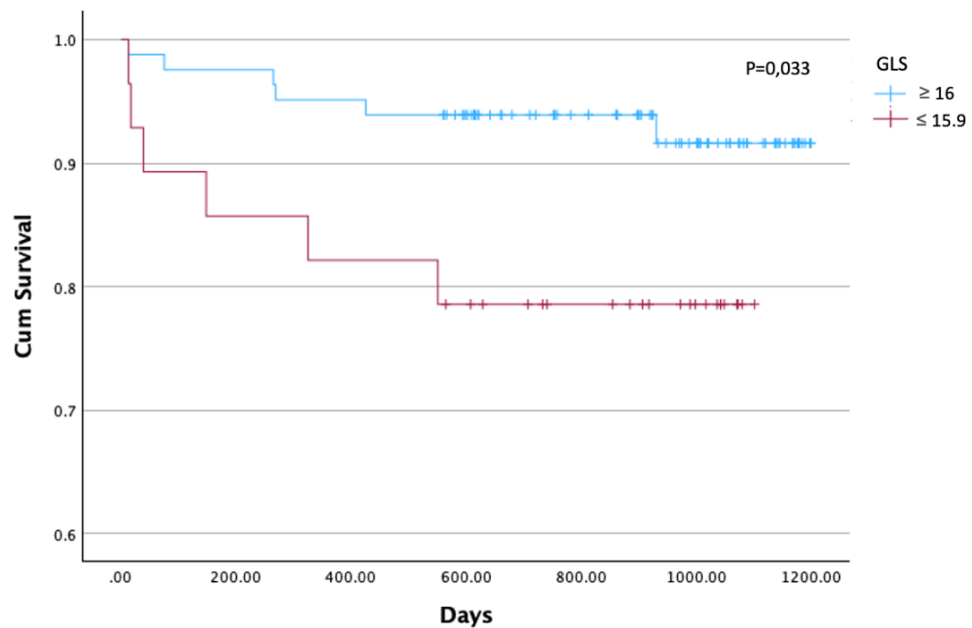
Figure 18. Kaplan-Meier event rate curves showing cumulative incidence of death in patients after ischemic stroke with abnormal Global Longitudinal Strain (GLS)

5. Discussion

The intricate interplay between the cardiovascular and nervous systems in the context of acute cardiac or neurological diseases is a pivotal area of clinical research that has profound implications for patient outcomes. This dissertation elucidates the complex relationship between acute neurological events and subsequent cardiovascular complications, providing insights into both the pathophysiological mechanisms and potential preventive strategies. Acute neurological events, such as strokes, are shown to significantly affect cardiovascular function. These conditions mimic myocardial infarction, making accurate diagnosis challenging yet crucial for appropriate management.

The work highlights the role of widely used biomarkers hs-cTnI and NT-proBNP, which are elevated in response to cardiac stress induced by acute neurological insults. In our work, more than 25% of patients exhibited myocardial

injury according to fourth definition of myocardial injury, from whom 15% of patients presented with dynamic change in hs-cTnI, noting high prevalence of acute myocardial injury. Myocardial injury was linked to both higher short-term mortality and unfavourable functional outcome. Stroke severity was associated both with chronic and acute myocardial injury. Additionally, acute injuries exhibited a more pronounced association with mortality short term. Our results are with accordance with other studies presenting cardiac enzyme elevation in patients after acute neurological diseases (92-94, 96-98). Troponins stand out as highly sensitive and specific biomarkers for detecting myocardial injury, demonstrating its efficacy. However, it is necessary to carefully assess the patient's history of ischemic heart disease and chest pain, especially when sudden circulatory deterioration occurs. Coronary angiography is very safe procedure to exclude the diagnosis of acute myocardial infarction with high certainty, caution is necessary due to the potential for haemorrhagic transformation when administering heparin. Although many stroke patients may not experience myocardial infarction, elevated cardiac enzymes can indicate myocardial injury and higher cardiovascular risk. Of the cohort, more than 65% of patients exhibited elevated NT-proBNP. The findings suggest that elevated NT-proBNP is associated with stroke severity, unfavourable functional outcomes, and short-term mortality in patients following acute ischemic stroke. Interestingly dynamic change is also important regarding patients mortality. However, we did not observe bigger effect in patients with more pronounced elevation comparing to patients with mildly elevated NT-proBNP. Other studies presented analogous or higher prevalence of NT-proBNP and their connection to stroke severity and poor outcome (101-104).

ECGs represent other feasible cost effective way to filter patients at risk, detecting possible myocardial impairment. ECG changes are quite common in patients after AIS, with more pronounced prevalence in patients with myocardial injury. Among most common changes, we detected T-wave inversion (21.2%), ST depression (15.2%), QTc prolongation (13.4%). No significant distinctions were observed between acute and chronic myocardial injury. Our numbers correlate with previous published studies where prevalent ECG changes were for T wave

inversion (15-35%), ST depression (25-33%), and a prolonged QT interval (20-35%) (7, 145). Other studies presented connection of prolonged QTc with decreased survival and worse neurological outcome (147). Moreover, associations were also established between ST depression and increased troponin levels (93). Atrial fibrillation (AF) emerged as most common arrhythmia in our work, prevalent in nearly one-third of patients. We did not observe any correlation between myocardial injury and the occurrence of atrial fibrillation. Atrial fibrillation, specifically, poses a risk for secondary complications such as ventricular tachycardia, heart failure, or cardiac death (146).

Regarding echocardiographic findings, global longitudinal strain (GLS) is a sensitive marker of myocardial dysfunction that could help predict risk for future events. Our findings suggest that stroke severity is not associated with abnormal GLS. However, we confirmed close relationship with positive hs-cTnI and connection with unfavourable outcome evaluated by mRS at 90 days. Moreover, patients with impaired GLS had higher overall mortality. LV Global Longitudinal Strain (GLS) emerges as a sensitive marker for detecting early myocardial dysfunction, even in patients with preserved LVEF. Findings suggests a correlation between stroke severity and LV dysfunction, with even mild impairment detected by 2D STE in the early stages. Abnormal GLS could be helpful predictor for clinical events and subclinical myocardial injury. This underscores the importance of integrated care approaches that consider echocardiographic examination in patients presenting with acute neurological events.

Our study underscores the importance of a careful assessment of patients to differentiate whether observed changes stem from neurological alterations or concomitant coronary artery disease. Dynamic ST segment changes, malignant arrhythmias, and fluctuations in cardiac enzyme levels suggest potential myocardial infarctions. However, these changes do not necessarily indicate the presence of a myocardial infarction but rather signify an elevated cardiovascular risk. Comprehensive evaluation, including early echocardiographic assessments to exclude wall motion abnormalities, is crucial for these patients. Patients exhibiting abnormalities during hospitalization should be considered for long-term cardiology

follow-up, ambulatory ECG monitoring, and regular echocardiography. Additionally, high-risk individuals with such changes may warrant further investigations, including CT coronary angiography, cardiac magnetic resonance imaging, or coronary angiography, to rule out ischemic heart disease.

Regarding novel biomarkers, findings position TRAIL levels as a significant prognostic indicator, with lower levels indicating a poorer prognosis—a correlation consistently observed in prior studies suggesting an increased risk of mortality. Various investigations have established a relationship between lower TRAIL levels and heightened mortality risk, especially in the context of cardiovascular diseases (115, 161). Our study further contributes to the understanding of TRAIL dynamics in acute stroke, revealing a consistent pattern of decrease in the acute phase, reaching its lowest levels within the first 24 hours of hospitalization, followed by a subsequent increase. In exploring the mechanisms by which TRAIL operates in the pathophysiology of stroke, we propose that cardiomyocyte injury may be influenced by autonomic dysfunction and elevated catecholamine levels, potentially leading to a decrease in TRAIL levels through the beta-adrenergic receptor. This novel insight suggests a complex interplay between TRAIL, autonomic dysregulation, and cardiovascular alterations.

The precise role of GDF-15 is not yet fully elucidated; however, it is primarily linked to metabolic regulation (122). It plays a significant part in the regulation of inflammation and both pro- and anti-apoptotic mechanisms within damaged and diseased tissues. Inflammatory conditions notably increase the expression levels of GDF-15 (123). Elevated GDF-15 levels are frequently observed in patients following acute ischemic stroke (AIS). Our study found that such elevations were associated with myocardial injury, poor functional outcomes, and all-cause mortality. Additionally, individuals suffering from more severe strokes exhibited higher levels of GDF-15. GDF-15 is becoming recognized as a biomarker for cardiometabolic risk and overall disease burden. Individuals with stable ischemic heart disease, acute coronary syndromes, heart failure (129), or atrial fibrillation (130) show elevated serum concentrations of GDF-15. These

levels serve as a promising indicator of adverse cardiovascular outcomes, providing predictive information that is independent of traditional risk factors.

Because Copeptin levels are positively linked to the severity of illness and eventual outcome, it has been suggested as a prognostic indicator in acute conditions. Apart from its documented connection with cardiac disease, copeptin appears to hold significance in various realms within cardiovascular health. A recent study highlighted elevated copeptin levels in individuals suffering from ischemic stroke. In our analysis, Copeptin elevation was associated with functional disability evaluated with mRS at 90days and with severe strokes, what is with accordance with other studies (141, 142). Even though, in other studies heightened copeptin levels upon admission correlate significantly with unfavourable outcomes and increase the risk of all-cause mortality, we did not confirm this result (141-144).

It is essential to acknowledge the limitations of our study. The study involves a sample size of 217 patients, which, while adequate for preliminary findings, may not be sufficiently large to generalize the results to a broader population. The study population is limited to patients from a single hospital, which may not represent the broader demographics and clinical characteristics seen in other regions or countries. Moreover, there is variability in the types of reperfusion therapies administered, which might introduce biases. Different treatments can have distinct impacts on biomarkers and outcomes. The study primarily focuses on the acute phase following a stroke, potentially overlooking long-term cardiovascular and neurological interactions and outcomes. At last, the variability in biomarker levels due to external factors (e.g., pre-existing conditions, medications) is not fully controlled, which could affect the study's conclusions.

6. Conclusion

In conclusion, the dissertation's findings emphasize the significance of a multidisciplinary approach in managing patients with acute neurological events due to the profound impact these events have on cardiovascular health. The

identified correlation between neurological severity and cardiac injury points out the necessity for vigilant cardiovascular monitoring in these patients. Preventive strategies should include aggressive management of traditional cardiovascular risk factors, such as hypertension and diabetes, which are prevalent in this patient population and contribute to the risk of cardiac complications. Implementing strategies that focus on early detection and management of cardiac complications could significantly improve clinical outcomes. Additionally, the use of biomarkers for early identification of cardiac injury could facilitate timely and targeted interventions, potentially mitigating the adverse outcomes associated with the heart-brain interplay. Biomarkers functions are intricate and context-dependent, impacting diverse pathways in different cell types and pathological situations. Our study reinforces the significance of negative prognostic marker for all-cause mortality and worse clinical outcomes following pathological processes. Notably, it sheds light on potentials as a predictors of stroke severity and poor short-term outcomes. Ultimately, this dissertation advances our understanding of the bi-directional influences between the nervous and cardiovascular systems during acute medical events. It calls for ongoing research to further delineate the mechanisms driving these interactions and to develop optimized therapeutic strategies that address the complexities of neuro-cardiological interplay.

7. Summary/Souhrn

Summary

Acute stroke can trigger various cardiac abnormalities, including arrhythmias, ventricular dysfunction, myocardial infarction, or sudden cardiac death. These issues often stem from disruptions in the autonomic nervous system (ANS). These conditions exhibit similar electrocardiogram (ECG) changes, cardiac function alterations, and elevated or decreased biomarkers. Our study focused on the interplay between the cardiovascular and the nervous system in acute stroke. In first part of the study we analysed dynamic changes of specific selected biochemical markers including hs-cTnI, NT-proBNP, Copeptin, GDF-15, TRAIL in patients

after acute stroke and its association with stroke severity, impact on the short-term outcome, and prevalence of cardiovascular involvement. In second part we evaluated subclinical electrocardiographic and echocardiographic changes, prevalence and impact on outcome. Results showed that changes in some biomarkers were associated with higher mortality, functional disability and stroke severity. Moreover, ECG changes were associated with subclinical myocardial injury. Regarding echocardiography, in global longitudinal strain analysis, lower strain was associated with higher mortality and disability. Results show that patients with subclinical myocardial impairment are at higher risk after stroke. This could help us identify these patients to offer them throughout cardiologic examination.

Souhrn

Akutní cévní mozková příhoda může vyvolat různé srdeční abnormality, včetně arytmií, dysfunkce komor, infarktu myokardu nebo náhlé srdeční smrti. Tyto problémy často pramení z narušení autonomního nervového systému (ANS). Tyto stavy se prezentují změnami na elektrokardiogramu (EKG), změnami srdečních funkcí a zvýšenou nebo sníženou hladinou biomarkerů. Naše studie se zaměřila na vzájemné působení kardiovaskulárního a nervového systému při akutní cévní mozkové příhodě. V první části studie jsme analyzovali dynamické změny specifických biochemických markerů, včetně hs-cTnI, NT-proBNP, Copeptinu, GDF-15, TRAIL, u pacientů po akutní cévní mozkové a jejich spojení se závažností iktu, dopadem na krátkodobý osud a prevalencí kardiovaskulárního poškození. Ve druhé části jsme hodnotili subklinické elektrokardiografické a echokardiografické změny, jejich prevalenci a dopad na osud pacientů. Výsledky ukázaly, že změny některých biomarkerů byly spojeny s vyšší mortalitou, funkčním postižením a závažností mozkové příhody. Navíc, EKG změny byly spojeny se subklinickým poškozením myokardu. Pokud jde o echokardiografii, analýza globálního longitudinálního strainu ukázala, že nižší strain byl spojen s vyšší mortalitou a postižením. Výsledky naznačují, že pacienti se subklinickým poškozením myokardu jsou po cévní mozkové příhodě ve vyšším riziku. To by nám mohlo pomoci identifikovat tyto pacienty a nabídnout jim komplexní kardiologické vyšetření.

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9. Publications

9.1. Publications

Mihalovic M, Tousek P. Myocardial Injury after Stroke. J Clin Med. 2021 Dec 21;11(1):2. doi: 10.3390/jcm11010002. PMID: 35011743; PMCID: PMC8745454.

Mihalovic M, Mikulenka P, Línková H, Neuberg M, Štětkářová I, Peisker T, Lauer D, Tousek P. Prevalence of myocardial injury in patients after acute ischaemic stroke according to standard criteria. Eur Heart J Suppl. 2023 May 24;25(Suppl E):E3-E9. doi: 10.1093/eurheartjsupp/suad104. PMID: 37234232; PMCID: PMC10206909.

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9.2.   Presentations

XXXII. Výroční sjezd ČKS 2024 – poster presentation

ESC Congress 2023 Amsterdam – poster presentation

Czech Cardiovascular Research and Innovation Day 2022 - presentation

ESC Congress 2022 Barcelona – poster presentation

ESC Heart and Stroke conference Budapest 2022 – poster presentation

ESC Heart and Stroke conference Prague 2021 – poster presentation

Students scientific conference on Third faculty of medicine 2021- Charles University – Dean's price for work