

OVERVIEW OF SOME CURRENT MEDICINE ISSUES

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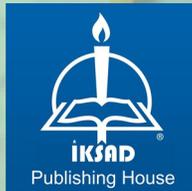
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CONTENTS

FOREWORD

Assoc. Prof. Dr. Bilge ASLAN1

CHAPTER 1

ANESTHESIA CARE DURING PROCEDURAL STROKE IN TRANSFEMORAL AORTIC VALVE REPLACEMENT

*Assist. Prof. Dr. Hülya YILMAZ AK, Dr. Yasemin ÖZŞAHİN,
Prof. Dr. Kerem ERKALP, Prof. Dr. Ziya SALİHOĞLU*3

CHAPTER 2

CARDIOVASCULAR COMPLICATIONS IN COVID-19

Assist. Prof. Dr. Saban ERGENE.....15

CHAPTER 3

POST-ANESTHESIA EMERGENCY DELIRIUM IN PEDIATRIC PATIENTS

Assist. Prof. Dr. Sule BATCIK.....43

CHAPTER 4

POST-ANESTHESIA EMERGENCY DELIRIUM IN GERIATRIC PATIENTS

Assist. Prof. Dr. Leyla KAZANCIOĞLU63

CHAPTER 5

INNOVATIONS IN CARDIOVASCULAR SURGERY

Assist. Prof. Dr. Sedat Ozan KARAKISI81

CHAPTER 6

NURSING MANAGEMENT OF COVID-19

Assist. Prof. Dr. Vacide Asik OZDEMIR111

CHAPTER 7

DETERMINATION OF SATISFACTION OF PATIENTS OVER 50 YEARS OF AGE WITH GENERAL HOSPITAL SERVICES IN THE SAMPLE OF 3RD STAGE UNIVERSITY HOSPITAL

Assist. Prof. Dr. Türev DEMİRTAŞ

Dr. Zekeriya TEMIRCAN.....127

FOREWORD

In our increasingly digital world, especially when it comes to current medical issues such as delirium, COVID-19 complications, cardiac support devices, patient satisfaction, it is important to make this information available in clinical practice, as well as to access accurate information. I hope this book will be useful to all my colleagues to update their basic medical knowledge and share various examples of how this knowledge can be used in the clinic. I would like to thank all the authors who contributed to the creation of the book and İKSAD Publications for the publication of the book.

Associate Professor Bilge ASLAN, 2021.

CHAPTER 1

ANESTHESIA CARE DURING PROCEDURAL STROKE IN TRANSFEMORAL AORTIC VALVE REPLACEMENT

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INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is an alternative to surgery in patients considered inoperable or at high risk (Howard et al., 2019). Moreover the U.S. Food and Drug Administration (FDA) approved an expanded indication for several transcatheter heart valves to include with severe aortic with severe aortic valve stenosis who are at low risk (<http://www.fda.gov/news-events/press-announcements>). TAVI, with its improved valve technologies will also be an option for patients in the near future and improved operator experience (Arsalan et al., 2016). Cerebrovascular events are among the most feared complications of TAVI, since they cause high morbidity and mortality (Lansky et al., 2016). Among these complications, the risk of cerebral embolism (CE), which can be encountered at a rate of ~3-4%, is higher compared to surgical valve replacement (Kappetein et al., 2012).



Figure 1: Cerebral angiography image of cerebral embolism after TAVI procedure

The choice of anaesthesia technique for TAVI may vary depending on the nature of the procedure to be performed, the patient's coexisting diseases, and the team's experience in the procedure. With the combination of local anaesthesia and sedation, monitored anaesthesia care (MAC) has advantages such as early detection of neurological complications, short surgery time, rapid recovery, and reducing the need for postoperative care (Yilmaz et al.; 2018; Franco et al. 2012; Fröhlich et al., 2014; Lambert et al.; 2019 ; Stagier et al., 2019). In the SOLVE-TAVI trial, ischemic stroke rates were found lower in the conscious sedation group's patients during TAVI because the neurological conditions of the patients are not masked by deep sedation or anaesthesia (Thiele et al., 2020).



Figure 2: Cranial computed tomography image of cerebral embolism after TAVI procedure

Safe sedation technique is difficult to achieve in elderly patients with severe comorbidities undergoing TAVI. BIS monitoring can effectively guide the depth of sedation during TAVI (He et al., 2017). The BIS algorithm is designed to process frontal EEG and detect suppression of brain activity (Kertai et al., 2012). The study of Mérat et al. suggested that the unexplained decrease in BIS may be a result of cerebral ischemia (Merat et al., 2001). Murakami et al. reported that the decrease in Near InfraRed Spectroscopy (NIRS) or BIS values may reflect the intraoperative global hemispheric ischemia that patients have undergoing CEA (carotid endarterectomy) (Murakami et al., 2020). On the contrary, Deogaonkar et al. examined the changes in BIS values in 52 patients who underwent awake CEA and found that only 1 out of 5 patients with neurological damage had a decreased BIS value. They concluded that BIS monitoring is unreliable for detecting cerebrovascular insufficiency (Deogaonkar et al., 2005).

It was reported that 80% of patients who underwent TAVI had newly formed silent cerebral ischemic embolic lesions detected by diffusion-weighted magnetic resonance imaging (DW-MRI) and these lesions affected two cerebral hemispheres and circulatory regions in most patients, who did not show any symptoms (Kahlert et al., 2010; Fairbairn et al., 2012). Although not always clinically apparent, these ischemic brain lesions have been associated with cognitive decline (Arsalan et al., 2016). Symptomatic SE is one of the mortality-related complications of cardiovascular interventional procedures and has been reported to increase mortality six-fold in TAVI cohorts

(Teitelbaum et al., 2019). Anaesthesiologists have an important role in detecting this complication, which affects both mortality and morbidity and is not uncommon and should direct them to early interventions that will prevent permanent neurological damage.

NIRS is used as a non-invasive cerebral monitoring technique that evaluates cerebral oxygenation. In a study conducted by Orihashi et al. with patients that underwent aortic surgery, a continuous decrease in regional cerebral oxygenation (rSO₂) values of patients, followed up with perioperative NIRS, was closely associated with the occurrence of postoperative neurological events (Orihashi et al., 2004). Studies in recent years have found a significant decrease in cerebral NIRS values during systemic hypotension deliberately created in the rapid ventricular pacing (RVP) phase of the TAVI procedure (Fanning et al., 2017, Seppelt et al., 2020). Cerebral complications and delirium risk may increase when NIRS values remain significantly low during RVP (Seppelt et al., 2020).

Cerebral embolic protection devices (CEPDs) have been developed to reduce the risk of CE and silent embolism. CEPDs aim to prevent tissue debris formed during the procedure from reaching the cerebral vasculature. CEPDs have been shown to be effective in filtration of debris and reduction of the volume of ischemic embolic lesions, hence their potential to reduce the clinically significant SE risk has been implicated (Bagur et al., 2017). CEPD is a promising technology, especially dual-filter CEPD can potentially reduce cerebral risk or neurocognitive dysfunction in TAVI patients with further

improvement (Fairbairn et al., 2012, Haussing et al., 2020, Bhandary et al., 2018, Seeger et al., 2019).

Frequent occurrence of new ischemic lesions associated with TAVI is 58-98%. A greater proportion of embolism (90%) occurs to the left hemisphere and posterior circulation due to the angulation between the aortic arch and left common carotid. However, the time of the emboli formation was correlated with the placement of the aortic valve prosthesis and TAVI implantation. If the emboli were in the vertebrobasilar system of the posterior circulation, the anesthesiologist should have easy access to the patient and the patient's airway management line since acute respiratory arrest and maybe cardiac event may occur (Fanning et al., 2018).

If CE is suspected, early diagnosis is both necessary and feasible. Both thrombolysis and embolectomy have been used to successfully treat CE following these procedures with positive clinical results (Wikholm et al., 2018). Currently, there are no guidelines for standard therapy for CE treatment following intravascular procedures (TAVI, coronary angiography, etc.). The nature of the embolism is variable (thrombus, aortic plate, fat, intravascular embolic debris, etc.) and some are more prone to thrombolysis than others. In addition, these patients may have a higher risk of hemorrhages (Mello et al., 2018). Peri-procedural and long-term thrombotic and bleeding events in the TAVI procedure also remain a concern, as there is no clear information about the type and duration of the optimal antithrombotic strategy (Lüscher et al., 2017).

Embolectomy has been proven to improve clinical outcomes in patients with proximal arterial occlusion for up to six hours from onset of cerebral ischemia. In some cases, this time can be extended up to 12 hours (Goyal et al., 2015). The success rate of the procedure increases with the experience of the neuroradiology team. Neurological deterioration that developed in our case was detected early, organized with the neurology and neuroradiology team, rapid imaging and early intervention were performed, and it was planned to be followed up with anticoagulant therapy. However, despite this treatment, there was no improvement in the neurological examination of the patient in the early period.

TAVI has become the most important treatment of choice in high-risk and elderly patients who cannot be operated on. In case the cardiac team performing the procedure is experienced, the need for general anaesthesia is often eliminated. However, the neurological complication rate of up to 80% during and in the days following the procedure, the long recovery period after embolism, the possibility of being a nursing patient and even the risk of death, remind us that the TAVI procedure and the sedation given during the procedure should never be underestimated. Unlike the patient under sedation, an awake patient and an experienced anaesthesia team take an active role in preventing and catching complications, so that the cardiac team can leave the paradox of saying "The procedure went well (the valve was placed well) but we lost the patient".

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CHAPTER 2

**CARDIOVASCULAR COMPLICATIONS
IN COVID-19**

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INTRODUCTION

Today, COVID-19 is continuing to exert an unprecedented impact on public health and health care delivery worldwide. Despite all measures, restrictions and vaccination programs, the devastating disease shows itself with new mutations and more potent variants. The numbers of newly diagnosed cases and deaths are still high. According to the World Health Organization (WHO) daily report, as of July 11, 2021, there are 186,232,998 confirmed cases and 4,027,858 total deaths (WHO1). The fourth wave has been increasingly seen in various regions of the world with new delta and lambda variants. Regarding the fight against the virus, critical issues such as resource allocation, hospital reorganization and prioritization of patients remain significant challenges. Besides the respiratory system, the disease has substantial effects on the other body systems, including cardiovascular, neurovascular and gastrointestinal systems. This chapter describes the commonly reported cardiovascular system complications due to COVID-19 in light of the current literature.

1. PATHOPHYSIOLOGY

SARS-CoV-2 is an enveloped, non-segmented and single-stranded positive-sense ribonucleic acid (ssRNA+) virus (Wu and McGoogan 2020). Angiotensin-converting enzyme 2 (ACE2) is a protein that is abundant in alveolar epithelial cells of the lungs, intestines, kidney, testis, gallbladder, and heart and is accepted as the entry site of SARS-CoV-2 (Hamming et al. 2004). ACE2 plays a critical role in

neurohormonal regulation of the cardiovascular system. SARS-CoV-2 virus easily binds to ACE2 receptor (Nicin et al. 2020). Inhibition of ACE2 leads to cytokine storms and can result in acute respiratory distress syndrome (ARDS) (Zhou P et al. 2020). At cellular level, the distinguishing feature of SARS-CoV-2 is a hyper-inflammation state mediated by cytokine storms. Cytokine storms occur as a result of irregular release of interleukin (IL)-6, interleukin(IL)-7 and the other cytokines and imbalance of the activation of T cells (Liu J et al. 2020). It has been reported that impaired immune system regulation and increased metabolic demand increase the risk of developing cardiovascular disease (CVD) related to COVID-19 (Wang et al. 2020). Viral disease increases cardiac demand by increasing cytokine activity, while systemic inflammation can destabilize vascular plaques (Kwong et al. 2018).

On the other hand, the virus itself may cause direct damage to the heart through ACE2 receptors found in the cardiac tissue (Chen L et al. 2020). In addition, COVID-19 leads to significant electrolyte abnormalities, predisposing patients to arrhythmias (Chen D et al. 2020). Patients with CVD may experience a more severe COVID-19 course (Li B et al. 2020). In a meta-analysis with 1527 COVID-19 patients, 17.1% of the patients had hypertension and 16.4% had CVD. These patients required critical care (Li et al. 2020). In a study by Wu et al. with 44672 COVID-19 patients, mortality rate was about five-fold higher among patients with co-existing CVD (Wu and McGoogan 2020). Critical COVID-19 patients may present with several

cardiovascular complications. Next section describes the most commonly encountered cardiovascular complications in COVID-19.

2. CARDIOVASCULAR COMPLICATIONS IN COVID-19

Cardiovascular system is negatively affected in COVID-19 through numerous physiopathological mechanisms caused by the virus, including coronary ischemia, cytokine storms, coagulopathy, hypotension, shock, pulmonary embolism and multiorgan failure. The most common cardiovascular complications in COVID-19 are shown in Figure 1.

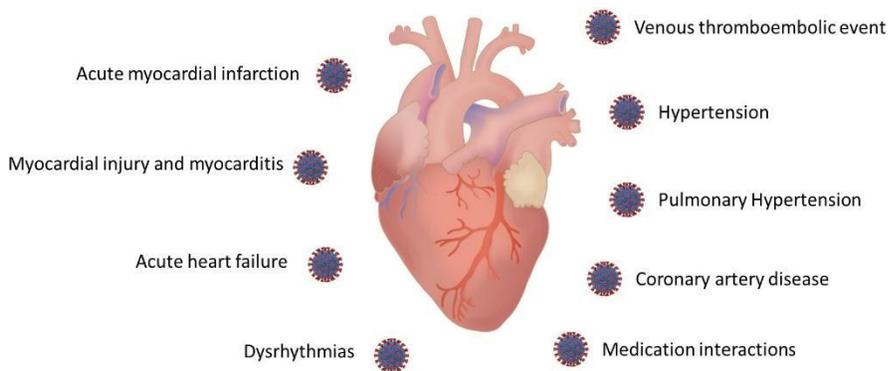


Figure 1. Common cardiovascular complications in COVID-19

2.1. Acute Myocardial Infarction (AMI)

Systemic inflammation in COVID-19 increases the risk for developing AMI (Guo et al. 2020). In addition, hypercoagulability also is a risk factor for AMI. During the pandemic, an increased coronary artery thrombus burden has been observed in STEMI patients (Roffi et al. 2020). Several case reports and case series have stated AMI secondary

to COVID-19 as shown by elevated cardiac markers (Capaccione et al. 2021). Studies have reported higher fatality rates for STEMI cases during the pandemic. In a study from Italy, the fatality rate of the STEMI cases was higher in 2020 compared to 2019 (De Rosa et al. 2020). However, AMI hospitalizations and catheterization laboratory activities have significantly reduced during COVID-19 pandemic. These reductions have been attributed to fear of being infected by the virus in the hospital and limited physical activities due to restrictions (Wilson et al. 2020).

AMI secondary to COVID-19 was named as COVID-AMI and defined as elevation of high-sensitivity troponin level above 99th percentile of normal range (Cameli et al. 2021). COVID-AMI has three potential etiologic factors:

- Plaque rupture or supply-demand mismatch
- Disseminated intravascular coagulation
- Non-ischemic injury

Differential diagnosis of COVID-AMI is challenging considering elevation of hs-cTn alone and clinical judgement, signs and symptoms, imaging and ECG changes should be taken into account (Cameli et al. 2021).

In COVID-19 patients, percutaneous coronary intervention (PCI) has been used as the treatment of choice in COVID-19 patients who develop AMI (Welt et al. 2020). On the other hand, conservative treatment may be sufficient in carefully selected COVID-19 patients.

Patients with AMI should also be assessed for the likelihood of COVID-AMI to employ safety measures when managing these patients.

2.2. Myocardial Injury and Myocarditis

Direct myocardial injury, hypoxia and increased physiologic stress cause myocardial injury and myocarditis with troponin elevation in viral diseases (Alhogbani 2016). Although mechanisms of myocardial injury in COVID-19 have not been fully understood, possible mechanisms have been proposed as direct damage to cardiomyocytes, systemic inflammation, hypoxia and myocardial interstitial fibrosis (Peng et al. 2020). Among the first reports of myocardial injury due to COVID-19, in a study by Huang et al. from Wuhan, China with 41 patients, high-sensitivity troponin I was elevated in 12% of the patients (Huang et al. 2020). Studies in the literature have reported myocardial injury in 7-17% of the hospitalized COVID-19 patients and 22-31% of COVID-19 patients in the intensive care units (Zhou P et al. 2020; Wang et al. 2020). In addition, elevated troponin I levels in patients with COVID-19 have been associated with the risk of adverse outcomes, including mortality. In a study by Shi et al. from Wuhan, China, 82 of 416 hospitalized COVID-19 patients showed myocardial injury (Shi et al. 2020).

Myocarditis is a clinical complication of myocardial damage and it can be diagnosed clinically or histologically. Myocarditis has also been associated with COVID-19. Myocarditis manifests a few days

after the onset of fever in COVID-19 patients. In a study by Ruan et al., 7% of deaths from COVID-19 were associated with myocarditis (Ruan et al. 2020). Presenting symptoms of COVID-19 can include chest pain, acute left ventricular dysfunction, dyspnea and dysrhythmias (Wang et al. 2020). In patients with COVID-19, ECG abnormalities are markers of severe disease and are associated with worse outcomes (Driggin et al. 2020).

2.3. Acute Heart Failure

Acute heart failure may be among the presenting manifestations of COVID-19. The incidence of acute heart failure is significant among COVID-19 patients and is associated with poor outcomes. The prevalence of new-onset heart failure among COVID-19 patients has been reported as 23% (Zhou F et al. 2020). In another study, heart failure was found in 24% of the patients and was associated with increased risk of mortality (Chen T et al. 2020). However, it is currently unknown whether acute heart failure is new cardiomyopathy or due to exacerbation of previous heart failure (Buzon et al. 2015). Right heart failure may also be seen in patients with severe ARDS and acute pulmonary injury (Murthy et al. 2020).

Imaging characteristics of congestive acute heart failure are similar to those of acute respiratory distress syndrome (ARDS) and include ground glass opacities and bilateral pulmonary infiltration. Therefore, echocardiography and serum BNP levels are used to confirm the diagnosis. COVID-19 may lead to decompensated heart failure and

lead to cardiogenic shock in the case of underlying cardiovascular disease (CVD) (European Society of Cardiology 2021).

Protecting against acute heart failure during COVID-19 is possible with early diagnosis and treatment of underlying diseases and the conditions that increase the risk for developing heart failure.

2.4. Dysrhythmias

A series of dysrhythmias have been reported in COVID-19 patients. Early studies have reported a high incidence of cardiac arrhythmias in COVID-19 patients (Wang et al. 2020). Dysrhythmias may be resulted from inflammatory stress, hypoxia and abnormal metabolism during the course of viral illness. The possible mechanism underlying dysrhythmias in COVID-19 are as follows:

- Cardiac injury due to viral infection
- Over-stimulation of immune system
- Prolongation of QTc interval
- Precipitated by other co-pathologies such as hypotension, pulmonary embolism, coronary plaque rupture, electrolyte abnormalities etc. During the course of COVID-19.

The most commonly encountered dysrhythmia in patients with COVID-19 is sinus tachycardia. Sinus tachycardia is likely to represent a physiological response to COVID-19. This dysrhythmia is accompanied by hypoperfusion, fever, hypoxia and anxiety (Driggin et al. 2020). In a study by Hamming et al., dysrhythmias were observed in 17% of the hospitalized COVID-19 patients and 44% of

those admitted to the ICU (Wang et al. 2020). In another study by Guo et al., ventricular tachycardia (VT)/ventricular fibrillation (VF) was found in 7% of the hospitalized COVID-19 patients (Guo T et al. 2020). In a study by Zareini et al. with 54 hospitalized COVID-19 patients, major arrhythmias were found by 28% with mostly being supraventricular tachycardias (Zareini et al. 2021). In a case series of 393 patients in New York city, atrial tachyarrhythmias were observed in about 7.5% of the COVID-19 patients (Goyal et al. 2020). These findings suggest likelihood of arrhythmias developing due to COVID-19 induced cardiac injury. Myocardial injury and acute myocarditis should be taken into account in the differential diagnosis in the case of dysrhythmias associated with elevated serum troponin level.

2.5. Venous Thromboembolic Event (VTE)

COVID-19 patients are at a high risk of developing VTEs consisting of deep vein thrombosis (DVT) and pulmonary embolism (PE) (Xie et al. 2020). VTEs and coagulopathy have been encountered as significant complications in COVID-19 patients. Risk factors for VTEs in COVID-19 include systemic inflammation, multiorgan dysfunction and abnormal coagulation. In addition, local vascular damage, coagulation and pulmonary thrombo-inflammation caused by COVID-19 infection increase the risk of VTEs. However, the pathogenesis of VTEs secondary to COVID-19 has yet to be fully understood.

Early reports of COVID-19 patients with coagulopathy have shown poor prognosis (Zhour F et al. 2020). In a study by Porfidia et al, the incidence of VTEs in COVID-19 patients was reported as 26% (Porfidia et al. 2020). Immobilization during the course of the disease also contributes to the development of VTEs. In a study by Zhang et al., it was reported that one in 10 consecutive COVID-19 patients may develop VTEs (Zhang et al. 2021). In a meta-analysis by Hasan et al., the prevalence of VTEs was reported as 31% in COVID-19 patients admitted to the ICU, despite anticoagulation (Hasan et al. 2020). In another study by Poissy et al., the prevalence of pulmonary embolism was significantly higher in ICU patients with COVID-19 compared to the patients admitted to the ICU due to other reasons (Poissy et al. 2020).

Elevated D-dimer levels have been reported in COVID-19 patients (Danzi et al. 2020; Tang et al. 2020). It has been reported that a D-dimer level $> 1 \mu\text{g/mL}$ was associated with increased risk of mortality in patients with COVID-19 infection (Zhou H et al. 2020). In patients with severe COVID-19 patients, anticoagulants, and especially low molecular weight heparin were associated with reduced mortality (Tang et al. 2020-2). COVID-19 patients should be administered thromboprophylaxis based on clinical features, body mass index, D-dimer level and creatinine clearance.

2.6. Hypertension

Studies in the literature have reported a significant association between hypertension and COVID-19 (Kulkarni et al. 2020). Hypertension triggers target organ damage and CVD that are determinant factors for COVID-19. Coronary artery disease, which is the main complication of hypertension, has been reported as an independent factor for mortality in COVID-19 patients (Li X et al. 2020). ACE downregulation by the novel coronavirus may be unfavorable in patients with baseline ACE2 deficiency including those with hypertension (Verdecchia et al. 2020). On the other hand, the use of renin-angiotensin-aldosterone system (RAAS) inhibitors such as ACE inhibitors and angiotensin receptor blockers (ARBs) may upregulate the expression of ACE2 and thus, facilitate worsening of the clinical status in COVID-19 patients (Sommerstein and Grani 2020).

In a study by Wang et al. with 138 COVID-19 patients, the prevalence of hypertension was found as 31.2% (Wang et al. 2020). In another study by Guan et al., patients with severe COVID-19 were reported to have significantly higher percentage of hypertension (Guan et al. 2020). In a review study by Rodilla et al. with 12226 COVID-19 patients from Spain, hypertension was the most common comorbidity by 50.9% (Rodilla et al. 2020).

Hypertension causes a number of pathophysiological alterations in the cardiovascular system, including fibrosis and left ventricular

hypertrophy. Therefore, a hypertensive heart is more susceptible to COVID-19. However, the relationship between COVID-19 and hypertension has not been yet fully understood. The presence of endothelial dysfunction has been proposed as the mechanism underlying this relationship. Endothelial dysfunction has been suggested to be involved in progression of COVID-19 due to atypical symptoms, including cardiac injury (Wang et al. 2020).

The peptides that are cleaved by ACE2 have been proposed to reduce inflammation and thus, have been recommended as a novel treatment method for hypertension. In a study by Meng et al., patients who used ACEi/ARB showed better outcomes regarding COVID-19 (Meng et al. 2020).

2.7. Pulmonary Hypertension

Pulmonary hypertension is defined as a mean pulmonary artery hypertension ≥ 25 mmHg at rest. Presence of pulmonary embolism can also contribute to occurrence of pulmonary hypertension. The altered endothelium in pulmonary hypertension may reduce the capacity to produce inflammatory response. Pulmonary hypertension is a physicoparhologic disorder that makes most CVDs and respiratory system disorders more complicated. Upregulated angiotensin II and low angiotensin 1-7 levels may cause increased pulmonary vasoconstriction and dysregulated hypoxic vasoconstriction mechanisms (Farha et al. 2020).

The presence of pulmonary hypertension has been reported to increase morbidity and mortality during COVID-19 (Zheng YY et al. 2020). However, the incidence of pulmonary hypertension in COVID-19 patients is lower compared to other cardiovascular complications. Studies from China, Italy and the USA have reported that the number of patients with pulmonary hypertension who get affected by COVID-19 is not too much (Ryan et al. 2020; Horn et al. 2020; Zhou H et al. 2020). In a study by Pagnesi et al., pulmonary hypertension was found in 12.0% of the hospitalized patients with COVID-19. In that study, pulmonary hypertension was associated with clinical, laboratory and imaging findings of severe COVID-19 infection and worse outcomes (Pagnesi et al. 2020).

Offensive features of pulmonary hypertension in COVID-19 are as follows (Hartopo et al. 2020):

- Altered immune system
- Reduced circulating ACE2 and angiotensin 1-7
- Increased endothelin-1
- Right ventricular dysfunction
- Altered cytokine production
- Altered levels of macrophages and neutrophils

The improved ventilation/perfusion mismatch and pulmonary vasodilatation through pulmonary vasodilators prevent patients from developing severe COVID-19 infection (Fernandes et al. 2020). The

protective features of pulmonary hypertension treatment in COVID-19 are as follows (Hartopo et al. 2020):

- Younger age
- Female gender
- Low body mass index
- Remodeling of pulmonary vasculature
- Altered levels of lymphocytes
- Reduced membrane ACE2 expression
- Chronic hypoxia
- Maintained left cardiac function

2.8. Coronary Artery Disease (CAD)

CAD is the most common cardiovascular disease and cause of mortality worldwide. The prevalence of pre-existing CAD in COVID-19 patients has been reported between 2.5% and 10% (Wu and McGoogan 2020). Patients with CAD infection by SARS-CoV-2 have a higher risk of adverse outcomes compared to COVID-19 patients without CAD (Yu et al. 2020). In a series of 44672 COVID-19 patients from China, underlying CAD was found in 4.2% of the patients (Yu et al. 2020). On the other hand, in a study by Pasquale et al. from Italy, underlying CAD was found in 40% of the patients (Di Pasquale et al. 2020). The proposed mechanisms underlying the effects of COVID-19 on CAD include the infection per se, cytokine storms, coronary spasm, hypoxic injury, microthrombi and an overactive immune system (Pedersen and Ho 2020; Tavazzi et al.

2020). Microthrombi due to coagulopathy and destabilized plaques lead to the development of obstructive CAD (Libby et al. 2018).

CAD develops in COVID-19 patients due to the activation of macrophages, increased thrombolytic tendency and impaired plaque stability because of systemic inflammation. Studies have reported that outcomes of COVID-19 are strongly associated with CAD (Madjid et al. 2020). COVID-19 infection triggers the development of cardiovascular diseases. Findings of studies in the literature suggest a bidirectional correlation between COVID-19 and CAD (Nishiga et al. 2020). High inflammatory burden during COVID-19 has been suggested to accelerate the development of cardiovascular damage (Tay et al. 2020).

Controlling the negative effects of COVID-19 on the cardiovascular system is one of the serious concerns, especially in patients with underlying CAD. High cardiac demand caused by tachycardia, hypoxia, fever, pain and anxiety may result in rupture, coronary artery plaque instability and acute coronary state. Therefore, reducing high cardiac demand, relieving fever and correcting hypoxia are recommended in this situation.

2.9. Medication Interactions

There are a number of medications studied for COVID-19 and many of them interact with other cardiovascular medications, including anticoagulants, antiplatelets, statins, antihypertensives and antiarrhythmics (Driggin E et al. 2020). Currently studied medications include corticosteroids, biologics, antivirals and antimalarials (Chavez

et al. 2020). Among these, ritonavir/lopinavir prolongs QT and PR, and interacts with antiplatelets, anticoagulants and statins (KALETRA). Hydroxychloroquine triggers electrolyte abnormalities, prolonged QT intervals and cardiotoxicity, and affects antiarrhythmic agents (Tönnemann et al. 2013). Methylprednisolone may lead to fluid retention and hypertension (Liu Y et al. 2020). Remdesivir may induce hypertension and arrhythmias. Favipiravir interacts with anticoagulants, statins and antiarrhythmics. Azithromycin may cause prolonged QTc, Torsades de pointes and dysrhythmias. Interferon may lead to direct myocardial toxicity, worsen cardiomyopathy and cause cardiac ischemia (Driggin E et al. 2020).

CONCLUSION

COVID-19 disease affects numerous organ systems, including the cardiovascular system, neurovascular system and gastrointestinal system, as well as the respiratory system. Cardiovascular complications induced by COVID-19 have been reported rather in the form of case reports and case series. The exact psychological mechanisms underlying the effects of COVID-19 on the cardiovascular system are unclear. There are only proposed possible explanations in the literature. This lack of knowledge affects the management of COVID-19 patients with cardiovascular complications. On the other hand, mechanisms of action are also not clear in cardiovascular disease as a risk factor for worsening COVID-19 outcomes. As new studies will be available, this gap in the knowledge will be closed and bidirectional relationships between

COVID-19 and cardiovascular complications will be more clearly elucidated.

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CHAPTER 3

**POST-ANESTHESIA EMERGENCY DELIRIUM
IN PEDIATRIC PATIENTS**

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INTRODUCTION

Emergency delirium (ED) was first described by Eckenhoff et al. in 1960s and is defined as disrupted awareness and attention of a child to environment accompanied with disorientation, hypersensitivity to stimuli and hyperactive motor behaviours (Eckenhoff et al. 1961, Nair and Wolf 2018). Although terms ED and emergence agitation (EA) are used synonymously in the literature, EA rather refers to hyperactivity state upon emergence from anesthesia, while ED is related to physiological dearengement (Wong and Bailey 2015). Diagnosis, treatment and management of ED is much more difficult, and ED term is usually used so as to encompass both. The highest incidence of ED is in children between 2-7 years of age, reported as about 20% (Lerman 2017, Nair and Wolf 2018). When pediatric ED is considered together with EA, the reported incidence varies in a wide range from 2% to 80% (Reduque and Verghese 2013). Thus, there is no exact consensus on the incidence of ED in the pediatric age group. The incidence of ED is higher in children than in adults (5.3%) (Shin et al. 2021). Signs and symptoms of ED manifest 30 minutes after the termination of anesthesia and last for 15 to 45 minutes. However, the symptoms may be persistent and have been reported up to 2 days (Holzki ve Kretz 1999). Although the etiology of ED is not fully understood, various risk factors have been associated with this condition (Kanaya 2016). Age, postoperative pain and exposure to short acting volatile anesthetics are among the risk factors.

It is critical to rule out the other causes in the diagnosis of ED. The child may be in pain upon emergence from anesthesia and therefore adequacy of anesthesia and appropriate treatment should be ensured with examination. In addition, other pathological causes of postoperative agitation and disorientation such as hypoglycemia and hypoxia should be considered before establishing the diagnosis of ED. ED is also a source of stress for caregivers, families and medical staff. Therefore, relatives of the child should be informed about ED preoperatively. This chapter begins with the etiology, risk factors and pathophysiology, and continues with the discussion of clinical picture, diagnosis, prevention, treatment and management of ED.

1. ETIOLOGY

The exact cause of ED is unknown. However, postoperative pain, pharmacokinetics and pharmacodynamics of anesthetic agents have been proposed as the causative factors (Dahmani et al. 2018). Sudden awakening to a disordered state of consciousness and unfamiliar environment is assumed to be a cause of ED (Reduque and Verghese 2013). Stimulation of the certain pathways, possibly in the amygdala and locus coeruleus by volatile agents at the neurodevelopmental stage of the brain has also been suggested as a cause (Viswanath et al. 2015). Rapid emergence from anesthesia is also among the factors associated with ED (Cohen et al. 2000). Postoperative disorientation and agitation may be caused by pain, hypoxia, hypercarbia, hypocarbia, hypotension, hypothermia, increased intracranial pressure, full bladder and urinary retention (Sikish and Lerman 2004). Apart

from the known risk factors, the incidence and severity of ED are still unpredictable.

Interest and concern in ED have emerged due to the use of volatile agents and perceived increase in the frequency of ED because of these agents in pediatric practice. In this setting, it has been suggested that the agents themselves, rather than rapid emergence, have some neuropharmacological stimuli against postoperative agitation in the immature nervous system as the cause of ED (Nair and Wolf 2018). Preoperative anxiety level also contributes to the development of ED. Kain et al. demonstrated that there was a 12.5% increase in behavioral changes of children with preoperative anxiety and each 10% increase in anxiety levels leads to a 10% increase in ED. In the same study, the authors stated that parents of anxious children also have anxiety and emphasized the importance of children and parents' education in the perioperative setting (Kain et al. 2006).

1.1. Risk Factors

Although there are numerous risk factors contributing to the development of ED, the most common factors included age, gender, temperament of the child, preoperative anxiety and behaviour, type of anesthesia, pain and type of surgery. As mentioned above, the peak incidence of pediatric ED occurs between 2-7 years of age. Patients in this age group are the most affected population. These children can not be reoriented to surroundings upon rapid emergence, which make children in this age group more vulnerable against ED (Vlajkovic and Sindjelic, 2007). Among preschool children, the incidence of ED is

higher in boys compared to girls. B:G rate was reported as 2:1 following surgical procedures under general anesthesia (Mohkamkar et al. 2014). Temperament of a child includes emotionality, sociability, activity and impulsivity and is an unchangeable factor. The incidence of ED has been found to be higher among more emotional and less social children (Nasr et al. 2011). Therefore, temperament of a child may cause different reactions to surroundings during emergence and the development of ED.

The probability of post-anesthesia ED is greater in children with preoperative anxiety symptoms. In addition, other behavioral disorders are also more common in these children (Kain et al. 2004). The most consistent risk factor of ED is the use of volatile agents. Rapid emergence from anesthesia increases the risk of developing ED. Relatively low ED incidence is obtained with total intravenous anesthesia (TIVA) applications. Although most studies in the literature have focused on sevoflurane, ED has been reported with all inhalational agents (Frederick 2016). Duration and depth of anesthesia seems to be not associated with ED.

Pain is a complex risk factor of ED. Although pain is not the main factor of ED, increased pain in the postoperative period is thought to be associated with an increase in the risk of developing ED. There are studies reporting that the use of opioids decreases ED incidence (Shi et al. 2015). Administration of proper perioperative analgesia decreases pain related ED behaviours in the recovery room. However, ED is also seen after painless procedures (Cravero et al. 2000). Higher

ED rates are reported following ENT operations (Lerman 2017). Mohkamkar et al. examined ED incidence in children following abdominal, orthopedic, urologic, ophthalmology and ENT surgeries and found that the highest rate of ED was seen after ENT procedures (Mohkamkar et al. 2014). However, according to some authors, the type of surgery is not expected to affect ED as long as an appropriate analgesia is applied (Abu-Shahwan 2008). A schematic description of the risk factors that cause ED in pediatric patients depending on the patient, surgery and anesthesia factors is given in Figure 1.

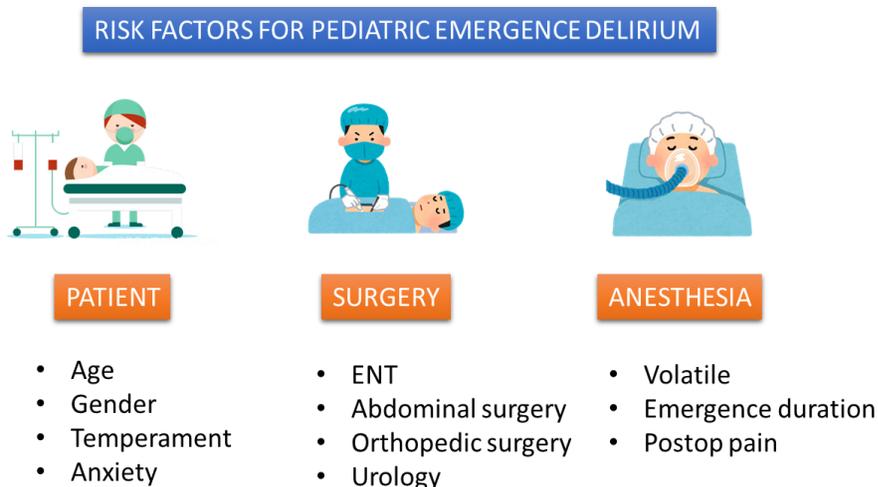


Figure 1. Risk factors of post-anesthesia emergence delirium in pediatric patients

2. PATHOPHYSIOLOGY

The pathophysiology of ED has not yet been fully elucidated. Many hypotheses have been proposed in order to explain the pathophysiology of ED. Among these, uncontrolled pain, preoperative anxiety and differential clearance of various volatile agents stand out

(Dahmani et al. 2014). Although severe pain is a predisposing factor, it is not recommended as a predictive measurement of emergence delirium, because ED may develop also in the absence of pain (Currie 2015). ED has been reported even in patients undergoing painless procedures such as MRI (Bonhomme et al. 2012). The imbalance between the extractive and inhibitory pathways and the differential effects of hypnotic agents on cortical and subcortical networks has been postulated. According to the clearance theory, various volatile agents are cleared from the central nervous system and this lead to changes in recovery rates of cognitive functions. Volatile agents interfere with the balance between neuronal synaptic inhibition and excitation in the central nervous system (Vlajkovic and Sindjelic 2007). Therefore, a patient with ED is “awakened”, although he/she cannot receive information from surroundings and cannot give response properly.

3. CLINICAL PICTURE

ED is thought to be a postoperative neurologic complication and is associated with physiological behaviours and preoperative anxiety. Classical risk factors in children related to preoperative anxiety include younger age, parent anxiety, not having many siblings, insufficient socialization and lack of previous medical experience. Similarities between these factors and the risk factors of ED indicate the presence of an association between these two conditions.

ED is usually defined as a motor agitation state with a confusion that does not recognize the environment. It typically begins at a short time after anesthesia and lasts for 30 minutes. Signs and symptoms of ED include inconsolable crying, uncontrolled movements and uncooperativeness. Children often tilt and kick with holding their head, can not establish eye contact and are inconsolable (Malarbi et al. 2011). Based on these specific symptoms, ED can be described as involuntary agitation with kicking, lack of eye contact with caregivers or parents and awareness of surroundings (Dahmani et al. 2014). These attributes may lead to negative effects on the child's parents and medical staff in both short-term and long-term.

Children may exhibit maladaptive behavioral changes in the late postoperative period. These changes are related to sleep disturbance, fear of loneliness, eating disorder, bed wetting and a high stress level for the parents. It has been reported that children with ED are 1.4 times more likely to develop maladaptive behaviors such as separation anxiety, sleep disturbance and eating disorder up to two weeks after surgery (Shin et al. 2021). In a study by Kain et al., it was found that all children undergoing general anesthesia showed negative behaviours up to two weeks after surgery, and these behaviours continued over 6 months in 20% and one year in 7% of children (Kain et al. 1996). Risk factors associated with these changes are similar to those for developing ED and include the presence of preoperative anxiety in the child and parents, sevoflurane based anesthesia, postoperative pain and ED (Fortier et al. 2010).

4. DIAGNOSIS

Clinical diagnosis of ED is established based on certain behaviours in the postoperative period. Children with ED are wandering around aimlessly and cannot make eye contact. They are confused and disorientated, can pull off monitors, IV lines, and dressings.

Several diagnostic scales have been developed for pediatric ED. One of the most popular scales, Paediatric Anaesthesia Emergence Delirium (PAED) was developed in 2004 and is recognized as a standard for the diagnosis of ED. PAED has a 64% sensitivity and 86% specificity (Sikich and Lerman 2004). Although PAED has been widely validated and is a highly effective diagnostic tool, it is not a quick and easy to use scale for clinical practice. In addition to PAED, Watcha and Cravero scales have also been developed as alternatives (Lee 2017).

The first priority before establishing the diagnosis of ED, is to assess children in order to provide their safety and to secure IV lines and dressings in their surroundings. The other causes of delirium should be assessed and excluded. Airway should be evaluated for patency and necessary steps should be taken if necessary. Respiratory patterns and chest movements of the child should be monitored. The child should be observed for respiratory failure and hypoventilation. Inadequate breathing or hypoventilation may be caused by central respiratory depression due to opiates or to insufficient return of muscle relaxants leading to hypercarbia and hypoxia. In this case, oxygen and

ventilation support should be provided. Blood pressure of the child should be checked. In addition symmetrical movements of all extremities should be assessed. The diagnosis of ED can be set after ruling out all the above mentioned causes (Lee 2017). Various life threatening conditions, including hypotension, hypercarbia, hypoglycemia and increased intracranial pressure may also lead to disorientation and altered mental status in the postoperative period. Therefore, these conditions should also be determined and treated promptly.

5. PREVENTION OF ED

The treatment of ED should ideally be preventive. Therefore it can be possible to avoid agitation and parenteral anxiety. Preventive strategies for ED include selection of appropriate anesthesia technique, premedication, and intraoperative administration of propofol, midazolam, dexmedetomidine, fentanyl and clonidine as multimodal analgesics. Effects of various anesthetics and analgesics in decreasing the incidence of ED have been widely studied in the literature (Nasr et al. 2011). However, these studies could not reveal a method that is superior to others. Comparison of the results among these studies is difficult as different assessment tools, surgery types and anesthesia types have been used. In addition to pharmacological methods, several non-pharmacological methods, including the presence of parents during induction and recovery, interactive games, music therapy etc. are helpful.

5.1. Pharmacological Prevention of ED

The incidence of ED can be decreased by modifying the anesthesia technique. Prophylactic ED prevention includes co-administration of sedatives and opioids, but the risk related to the use of these agents must be weighed against the self-limiting nature of delirium. Pharmacological measures to prevent ED include addition of medication such as perioperative analgesics and decreasing or avoiding the use of volatile agents such as sevoflurane and desflurane. Low blood gas solubility of volatile agents lead to a rapid emergence from anesthesia that is harmful for children. Systemic or regional administration of many sedative and analgesic agents is known to be effective in prevention of ED. These preventive treatments include propofol at the end or during surgery, intraoperative fentanyl, systematic or regional ketamine, dexmedetomidine, midazolam clonidine, preoperative gabapentin, and dexamethasone etc. (Dahmani et al. 2014). Among these agents, the blood level of propofol is below therapeutic effects since it has a short half-life (Dahmani et al. 2010). These preventive agents have been compared in various studies in order to determine the most appropriate agents for ED. Clonidine and melatonin were found to reduce the incidence of ED (Kain et al. 2009). Dexmedetomidine administered at the end of surgery or as a continuous agent was reported to be superior over the administration of propofol bolus at the end of the surgery or continuous administration of ketamine (Ali and Abdellatif 2013). Although dexmedetomidine increased the length of stay in PACU, its

analgesic and anesthetic effects cause it to be preferred in prevention of ED. Dexmedetomidine has a high affinity for alpha2-receptor and it decreases the release of norepinephrine from the CNS. Activation of alpha2 receptor leads to analgesia, sedation, hypotension and bradycardia. Another advantage of dexmedetomidine over the other agents is its versatility in all phases of the perioperative period. Preoperative, intraoperative and postoperative uses of these agents have been reported to be successful. In addition, dexmedetomidine has a low side effect profile (Cao et al. 2016).

5.2. Non-pharmacological Prevention of ED

Non-pharmacological strategies for the prevention of ED have focused on the management of preoperative anxiety because of the strong association between preoperative anxiety and ED. Numerous successful strategies have been developed for preventing the development of ED in pediatric patients. Among these are quiet induction with decreased sensory stimuli, music therapy, distraction of attentions and hypnosis, clowns and videos before the inductions (Yip et al. 2009). In addition, the presence of parents during and after induction has been found to be effective in reduction of ED (Lardner et al. 2010). In a study by Kain et al., it was found that informing the parents about the methods and enrolling them in the distraction of their own children during the induction of anesthesia and while in the waiting room was more effective than premedication with midazolam in preventing ED (Kain et al. 2007). Also watching cartoons or playing video games was reported to decrease the incidence of

children in some patients as effectively as premedication with midazolam (Kerimoglu et al. 2013).

Acupuncture can also be an important technique in reduction of ED. In a double-blind randomized controlled study from Japan, electrical stimulation with a peripheral nerve stimulator on the heart region was shown to decrease ED (Hijikata et al. 2016).

6. Treatment and Management

The diagnosis of ED is established clinically at the first stage. The diagnosis is based on specific symptoms and enables ruling out the other causes including pain, respiratory failure and hemodynamic instability. The decision whether or not to treat ED with additional medication depends on the severity and duration of the symptoms. Many studies have shown that ED is a self-limited condition and resolves spontaneously without any pharmacological intervention over time (Voepel-Lewis et al. 2003, Cole et al. 2002).

Treatment should be administered in the case of agitation with the risk of injury. Pharmacological treatment of post-anesthesia ED includes intravenous administration of sedative agents such as propofol and midazolam, and opioid agents such as fentanyl (Hallen et al.. 2001). These agents are administered intraoperatively or at the end of the surgery. Midazolam IV 0.02-0.1 mg/Kg, fentanyl IV 1-2 µg/Kg and propofol IV 0.5-1.0 mg/Kg were demonstrated to be effective (Vlajkovic and Sindjelic, 2007). However, it should be kept in mind that these agents may prolong the length of stay in PACU.

When managing ED, necessary measures should be taken to provide safety for children and prevent them from harming themselves. Availability of more than one caregiver is often necessary. Since the child can be upset with stimuli in the environment, it is important to provide a quiet and darkened recovery room (Moos 2005). Reuniting the child with the parents as soon as possible after the surgery is one of the most effective strategies.

CONCLUSION

ED is a common complication in anesthetized children. It can be disturbing for children, parents and medical staff, but this condition is self limiting. Preventive strategies include the prevention of preoperative anxiety, relieving postoperative pain, and pharmacological management intraoperatively and at the end of the surgery. However, although adjuvant medication decreases the risk of developing ED, it may prolong the duration of recovery. Further studies are needed to investigate the best strategy in order to minimize adverse effects of anesthesia on emergence delirium. In the case of ED, parents should be informed about maladaptive behaviours of the child that can occur within weeks or months after the surgery.

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CHAPTER 4

**POST-ANESTHESIA EMERGENCY DELIRIUM
IN GERIATRIC PATIENTS**

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INTRODUCTION

The number of elderly patients who require surgical intervention and procedures is increasing in parallel with the ageing global population. Proper management of geriatric patients contributes to the reduction of complications that increase an increase in healthcare costs. Therefore, this age group has been increasingly a focus of interest in recent years (Benavides-Caro 2016). A different approach is needed for understanding age related physiological, anatomic, social and lifestyle differences in order to provide the optimal management for treatment of these patients.

Mental disorders following surgery has been subject of interest for years. Acute confusional state, known as delirium, is one of the most commonly encountered postoperative complications. The word ‘delirium’ originates from a Latin term, which means ‘off track’ (Saxena and Lawley 2009). Although a variety of terms are used for delirium in the literature, including “acute confusional state”, “acute cerebral syndrome”, “acute cerebral failure” and “toxic-metabolic encephalopathy”, today delirium is preferred to describe this condition (Morandi et al. 2008). Delirium is defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) guidelines as “impaired attention, awareness and cognition that develops in a short time and fluctuates throughout the day (Patel et al. 2017).

Postoperative delirium may lead to increased morbidity, delayed functional recovery and prolongation of hospitalization in elderly patients. In postoperative delirium, patients think and speak incoherently, are disoriented and exhibit impaired memory and attention. It has been reported that mortality is about two times higher in the case of delirium compared to patients without delirium (Cole and Primeau 1993). The incidence of delirium is nearly 15% in geriatric patients undergoing major procedures, but this rate may be much higher in the case of cardiac procedures and hip fracture surgery (Rudra et al. 2006). This chapter discusses etiology, epidemiology, diagnosis and management of post-anesthesia emergence delirium in geriatric patients. In addition, future considerations on this subject are also included.

1. ETIOLOGY

The mechanisms causing delirium are controversial. There is no common pathway for delirium, and it is rather a result of the symptoms of multiple neurotransmitter abnormalities. According to a proposed hypothesis, the mechanism underlying delirium is decreased oxidative metabolism in the brain, resulting in reduced neurotransmitter levels and leading to mental dysfunction. Another hypothesis suggests that increased serum levels of cortisol due to surgical stress are responsible for postoperative delirium (Chung 1997). The etiology of delirium is multifactorial. It has been reported that 90% of patients with postoperative delirium have three or four

determinable etiologic factors, while 27% have two identifiable factors and 16% have only one etiologic factor (Camus et al. 2000).

Predisposing factors in geriatric patients make these persons more susceptible to the development of delirium. Among these factors are age, male gender, severity of physical disease, hip fractures, stroke, functional dependency, neurologic disorders, depression, immobility, dehydration, metabolic abnormalities and alcoholism (Staus 2011). Whereas, triggering factors are acute mechanisms leading to delirium and include pain, anemia, hospitalization in intensive care unit, medications, sleep deprivation, hypoxemia, bladder catheter, electrolyte abnormalities and surgery itself (Kocabasoglu et al. 2012).

1.1. Etiology of Delirium in Geriatric Patients

Elderly people are more susceptible to the development of delirium due to age-related losses in the cholinergic reserve that is needed for memory, learning, attention and awareness (MacLulich et al. 2008). The most important risk factor for delirium in this age group is dementia, and two-third of elderly patients with delirium have comorbid dementia (Fong et al. 2009). Both dementia and delirium are associated with cholinergic deficiency and decreased cerebral blood flow. The most common causes of delirium in this group of patients include endocrine causes, systemic effects of neoplasms and drug intoxication (Leentijens et al. 2008).

2. EPIDEMIOLOGY

Delirium is a common and serious condition in elderly and affects 30% of this population, especially in hospitalized patients (Saxena and Lawley, 2009). The prevalence of delirium is reported as 10-31% at the time of admission and 3-29% during hospitalization (Siddiqi et al. 2006). The risk of developing delirium in these patients increases in intensive care units with a prevalence, which may rise to 80% (Morandi and Jackson 2011). Higher rates have been reported in surgery settings. An incidence up to 70% is reported especially following surgeries such as cardiothoracic surgery, vascular surgery, emergency procedures including hip fracture orthopedic operations and cataract removal (Guebther and Radtke 2011).

3. POST-ANESTHESIA EMERGENCE DELIRIUM

Emergence delirium (ED) was described for the first time by Eckenhoff et al. who examined more than 14000 patients who exhibited unusual behavioral disorders following surgery (Eckenhoff et al. 1961). Geriatric patients are more vulnerable to ED as a result of several organic factors, including hyponatremia, hypokalemia and toxicity from anesthetic medications. Delirium is a frequently seen complication in elderly patients and is classified as ED and postoperative delirium (POD) based on the onset time in the postoperative period. ED is also referred to as “emergence agitation” (EA) or “post-anesthetic excitement”. ED occurs immediately after surgery and lasts for 5-15 minutes (Burns et al. 2004). ED manifests

more commonly as excitement in young patients and somnolence in elderly. However, the onset interval of ED is highly variable (upon awakening, first minutes, first hours, days or weeks), which make classification of this form of delirium difficult. ED is seen immediately after emergence from general anesthesia. ED is thought to be associated with the influence of general anesthetics and is self-limited without leaving sequela (Radtke et al. 2010). ED can be suddenly dangerous in post-anesthesia care units (PACU), leading to serious consequences for the patient such as injury, catheter removal that requires physical or chemical restraints, hemorrhage, increased sense of pain, and self-extubation. In addition, ED may be disturbing for anesthetists and other medical staff, which may further increase hospital costs (Duffen and Williams 2011).

So far, there is no precise definition and timeline for ED. Protocols used for the definition and measurement of ED show high variability among different healthcare centers (Gooden et al. 2014). Furthermore, since there is no scale or guidelines for ED seen in PACU, patients in PACU are usually approached similar to those in intensive care units. Failure to consider pharmacokinetic and pharmacodynamics in sedated elderly patients, may lead to overdose that triggers anesthesia-related cognitive alterations and ED. ED-related complications accounts for 3-5% of ann perioperative complications (Rose 2015). ED is associated with perioperative outcomes including pulmonary complications, prolonged hospital stay and high readmission rates. The risk of developing POD and poor outcomes has been reported to

be higher in geriatric patients with ED (Zhang et al. 2020). ED complicates hospitalization of more than 2.3 million elderly people annually (Assefa et al. 2020).

Among the risk factors for developing ED in geriatric patients, there are several sociodemographic factors, including age, lack of a stable partner and educational level. In addition, severe postoperative pain is another related factor. In a study by Carrilo and Medrano, it was suggested that a higher rate of ED may be seen especially in patients aged over 80 years, probably due to increased susceptibility because of decreased cerebral plasticity and density with ageing (Carrilo and Medrano 2011). In addition, anesthesia has been reported to play a key role in the mechanism of delirium that triggers neuro-apoptosis in these patients (Monk and Price 2011). In a study by Alvares-Bastidaz et al., risk of experiencing emergence delirium was shown to increase by approximately 6 fold in patients aged over 70 years (Alvares-Bastidaz et al. 2018).

Anesthesia technique used is known to be associated with the occurrence of ED. However, there are studies reporting no significant difference among anesthesia techniques in terms of ED. On the other hand, in a study by Hernandez and Sanchez, the use of general anesthesia was found to be associated with delirium compared to neuraxial anesthesia (Hernandez and Sanchez 2014). Similarly, some studies have reported decreased incidence of ED in operations performed under regional anesthesia (Mason et al. 2010). Conversely, in a study conducted in 2016, a similar incidence of delirium was

reported between general anesthesia and neuraxial block. The authors concluded that the presence of delirium was associated with the suppression of cerebral activity at a high level as determined with electroencephalography regardless of anesthesia technique (Guenther et al. 2016). The files of more than 12000 patients undergoing surgery under general anesthesia were examined and it was found that more than 10% of these patients experienced mental decline and cognitive dysfunction, and a high incidence of emergence delirium was reported in elderly patients. Therefore, general anesthesia technique was recommended to be reserved for emergency operations (Bedford 1995).

Inadequate pain management has also been associated with ED (Jankowski et al. 2011). In a study by Alvares-Bestidaz et al., severe pain with a VAS score >7 was reported to increase the probability of delirium by five times (Alvares-Bestidaz et al. 2018).

4. DIAGNOSIS

Because ED is a complex syndrome with a variable clinical picture, clinicians should maintain a high suspicion index in order to detect post-anesthesia delirium promptly. ED exhibits acute and subacute changes from the baseline values and so, basal cognitive status of each individual patient should be carefully documented in the preoperative period (Katie et al. 2016). The diagnosis of ED is based on history, physical examination, laboratory analysis and radiographic findings.

Other neurocognitive disorders that should be ruled out to establish the diagnosis of ED are shown in Figure 1.

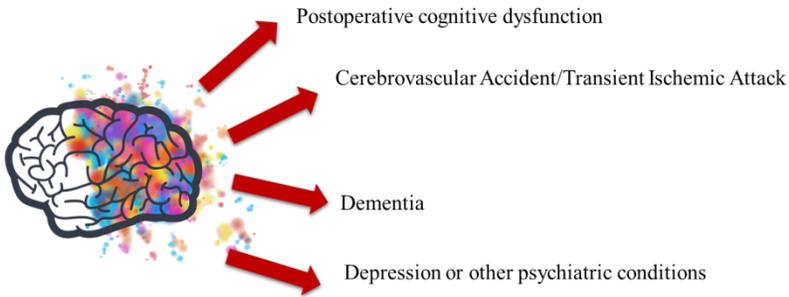


Figure 1. Differential diagnosis of emergence delirium

5. MANAGEMENT OF ED IN GERIATRIC PATIENTS

There is no established treatment for ED. However, a careful approach in the perioperative period can reduce its severity and incidence. All medical staff should exert a serious effort in order to ensure security of both patients and personnel (Hatzakorzian et al. 2006). The development of ED in geriatric patients can be reduced by timely detection of the risk factors and taking preventive measures. Prevention, screening and early treatment are the key points of the management of ED. In a meta-analysis by Moyce et al., lighter anesthesia was found to be effective in the reduction of post-anesthesia delirium (Moyce et al. 2014). In a randomized controlled study, a proactive geriatric consultation was found to decrease the incidence of ED by one-third following hip-fracture repair operation (Marcantonio et al. 2001).

In the case of the identification of ED, patients should not be transferred from the recovery room to the ward before initiating etiology and symptom based treatment, because delayed treatment leads to a higher mental decline (Saczynski et al. 2012). Possible etiologic factors in geriatric ED include anxiety, pain, presence of tracheal tube, bladder distention and urinary retention and the need for urination despite indwelling catheter. Tracheal tube should be removed in awakened patients as soon as possible since it would cause stress.

Residual neuromuscular block can be frightening in terms of ED; however, proper monitoring of neuromuscular block during surgery and in PACU will decrease the risk of residual block. Once a residual neuromuscular block is detected, patients can be antagonized. Antidepressants have been reported to be a protective factor for delirium. This is possible due to anxiolytic properties of these drugs and a long half-time that involves entire surgery (Lepouse et al. 2006).

Benzodiazepines are prescribed because they alleviate anxiety, and these agents are expected to protect against delirium. However, they are known to have various paradoxical effects such as irritability, aggression, and confusion. Several studies have reported more common delirium in elderly patients receiving benzodiazepines, but there is no study reporting especially the incidence of ED (Kudoh et al. 2004). On the other hand, in a prospective study by Schor et al.,

benzodiazepines were found to provide protection against delirium in patients hospitalized for surgery or other reasons (Schor et al. 1992).

According to 2017 guidelines by the European Society of Anaesthesiology, perioperative management of delirium is performed as follows (Aldecoa et al. 2017).

Preoperative Assessment:

- Assess the risk factors
- Avoid the use of benzodiazepines and pre-medication except for anxiety
- Avoid anticholinergic medications
- Minimize fluid fasting duration
- Consider alpha-2 agonists
- Maintain day-night rhythm
- A detailed pre-evaluation is needed in geriatric patients

Anesthesia:

- Avoid benzodiazepines except for withdrawal
- Proper pain control, continuous opioid infusion
- Monitor anesthesia deep and avoid deeper anesthetic levels

Recovery Room:

- Non-pharmacologic measures such as help for orientation, visual/hearing issues, noise reduction and sleep facilitation
- Assess pain

- Treat the underlying cause, if possible
- A detailed post-operative assessment is needed

6. FUTURE DIRECTIONS

In the American Geriatrics Society, Delirium Best Practice panel, anesthesia depth was found to be the only intraoperative intervention for ED (Schenning et al. 2016). This does not mean that the other factors including medications, hemodynamics and cerebral saturation have no effect on delirium, and indicates the necessity of future high quality and comprehensive studies. Based on a pilot study conducted about anesthesia depth in patients with hip fractures, anesthesiologists were recommended to avoid using deep anesthesia plans.

Geriatric ED is a possible result of a combination of oxidative stress processes and neuroinflammation. Therefore, studies are ongoing regarding noradrenergic, inflammatory, anticholinergic and ischemic markers (Stoicescu and McVicker 2014). High postoperative norepinephrine levels were found in patients developing ED (Deimer et al. 2014). In addition, genetic factors that predispose geriatric patients to ED are a new field of research for future studies.

CONCLUSION

Emergence delirium is a common complication in geriatric patients, and is independently associated with increased morbidity and mortality. Especially in geriatric patients, etiologic factors and underlying mechanisms of ED are highly variable, making the

management of ED challenging. A successful management of ED requires timely identification of patients at risk of developing ED and a proactive approach for the diagnosis and treatment.

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CHAPTER 5

INNOVATIONS IN CARDIOVASCULAR SURGERY

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INTRODUCTION

Cardiovascular surgery is a medical discipline that requires continuous innovation. Innovation in cardiovascular surgery aims to improve efficiency and outcomes of surgical cardiovascular interventions, to increase success rate and patient satisfaction and to enhance patients' quality of life, while reducing operational costs. In parallel with technological advancements, less invasive techniques are being used more widely. On the other hand, developments in imaging studies also contribute to innovative approaches. It is obvious that machine learning and deep neural networks among the components of artificial intelligence (AI) will play an increasingly critical role in the area of cardiovascular surgery in near future. However, despite all innovative approaches and therapeutic solutions, there are still numerous challenges that require sustainable innovations in cardiovascular surgery. It is expected that especially complex cardiovascular surgeries will be performed with much smaller incisions, greater precision, and targeted organ approaches using novel techniques and enhanced procedures in the next 50 years owing to innovative developments. Surgeons can be innovative by following new research and development and using innovative approaches in clinical practice.

Near future is open to sustainable innovations in the field of cardiovascular surgery. While artificial intelligence (AI) applications will increase accuracy of imaging modality and prediction of patient outcomes and complications, nano-technology and robotic surgery will enable more efficient surgical techniques, modifications, less

invasive interventions, and advancements in digital technology will pave the way for more intensive use of remote robotic surgery, and tele-medicine will allow facilitate follow-up. In this chapter, different definitions of innovations are given briefly, medical innovations are described and the most significant examples of innovation in cardiovascular surgery are discussed.

1. WHAT IS INNOVATION?

Innovation is defined as the provision of more effective or better technologies, products, processes, services and ideas that are adopted by society, markets and individuals (Wikipedia 2021). The word ‘innovation’ is derived from Latin word ‘innovare’ that means “into new” (Lin 2006). Innovation is associated with invention, but is not the same. Innovation involves practical application of an invention, but a new invention is not mandatory in innovation (Kogabayev 2017). Innovation is a cumulative process consisting of a wide spectrum of decision-making processes ranging from generating a new idea to the implementation stage. However, there is still no generally accepted universal definition of innovation. According to Twiss and Goodridge, innovation is a process combining technology, science, management and implementation to achieve an improvement or novelty in services, products and technologies (Twiss and Goodridge 1989). In otherwords, innovation is a process involving transformation of an opportunity into new ideas. Innovation is the implementation of new practical tools and techniques that improves or replaces the existing products, services, processes and techniques. Innovations in

products, services, techniques, finance and labor utilization are crucial to improve performance and results (Dutta et al. 2010). Definition of innovation also widely varies according to the field of interest. In the healthcare area, innovation is defined as the introduction of new ideas, services, processes, techniques or products in order to improve diagnosis, treatment, education and research. Healthcare innovations aim at improving safety, quality, efficiency and costs in the long-term (Omachonu and Einspruch 2010).

2. INNOVATION IN MEDICINE

Innovation in the field of medicine has been fueled by enhanced public health approaches, ongoing medical R&D studies, and increasing role of information technologies. It is estimated that medical innovations such as mobile applications and artificial intelligence will change the delivery of medical services in both developed and developing countries (Global Innovation Index 2019). Medical innovation is multidimensional and involves complex factors that influence how innovations will be disseminated and implemented (Greenhalgh et al. 2005). Medical innovation aims to add value to health systems, products, services and technology through improved safety, efficiency, quality, affordability and sustainability (WHIG). Many medical innovations took place between 1940 and 1980 and included cardiac procedures, chemotherapy, radiation, vaccines, antibiotics and medical devices such as artificial joints (Sampat 2019). A growing number of people can increasingly access improved healthcare via innovations. This has largely been resulted from the

raise of global healthcare expenditure, which has been reported as 7.6 trillion USD in 2018, corresponding 10% of global GDP (Deloitte 2018). Novel drugs, diagnostic and surgical techniques have helped millions' of people to live longer and improved quality of life (Laal 2011).

Medical innovations can be classified in three groups:

- Medical devices: Numerous novel medical devices contribute to treatment of different diseases and conditions.
- Technology: Innovations in medical technology enable us to diagnose and treat medical conditions more effectively.
- Medications: Some of the best medical innovations have been made in the area of drug therapy.

The history of modern medicine is full of sustainable innovations. Only a few examples of breakthrough medical innovations throughout the history include artificial hearts, handheld scanners, dialysis device, laser surgery, organ transplant, nano-healing, X-ray, electrocardiography, echocardiography, computed tomography (CT), magnetic resonance imaging (MRI), mammography, ultrasound, robotic catheters, bone drills, lenses, artificial joints, penicillin, aspirin, statins, insulin, oral contraceptives and viagra. Innovation occurs following several consecutive stages as depicted in Figure 1.

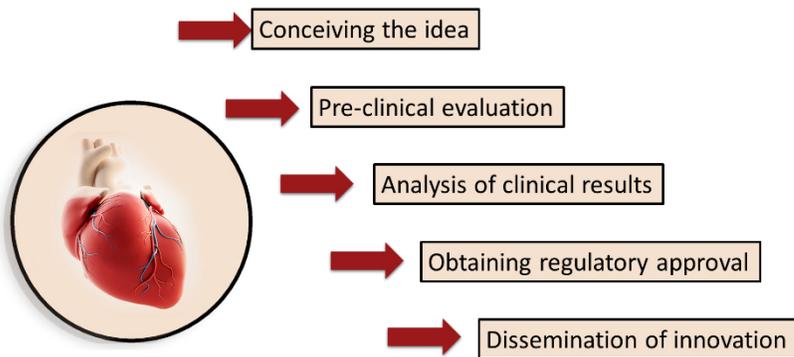


Figure 1. Phases of medical innovations

3. INNOVATION IN CARDIOVASCULAR SURGERY

Transforming new scientific ideas to clinical practice is one of the most rewarding and exciting experiences in medicine. Cardiovascular surgery specialty has been one of the fields of continuous innovation since early times when the heart-lung machine, namely cardiopulmonary bypass was successfully applied in the 1950s (Dearani et al. 2019). A surgical procedure or operation that has documented mortality rates is usually the gold standard by which new approaches will be compared. Surgical innovations have improved outcomes, reduced hospitalization time, and decreased the rates of complications, morbidity and mortality. For example, one of the breakthrough innovations, minimal invasive surgery has decreased postoperative pain and surgical trauma, and shortened recovery time with smaller incisions. However, cardiovascular diseases have been the leading cause of mortality and morbidity worldwide despite novel approaches (de Abreu et al. 2021) and there are still a wide range of clinical challenges requiring innovation in cardiovascular surgery

discipline (Cosgrove 2000). It is expected that especially complex cardiovascular operations will be performed with greater precision, much smaller incisions and targeted organ approaches in the next 50 years owing to innovative developments (Cerfolio et al. 2017).

Figure 1 shows important innovations in cardiovascular surgery. Examples of the most significant innovations in the field of cardiovascular surgery are discussed in the next sections of this chapter.

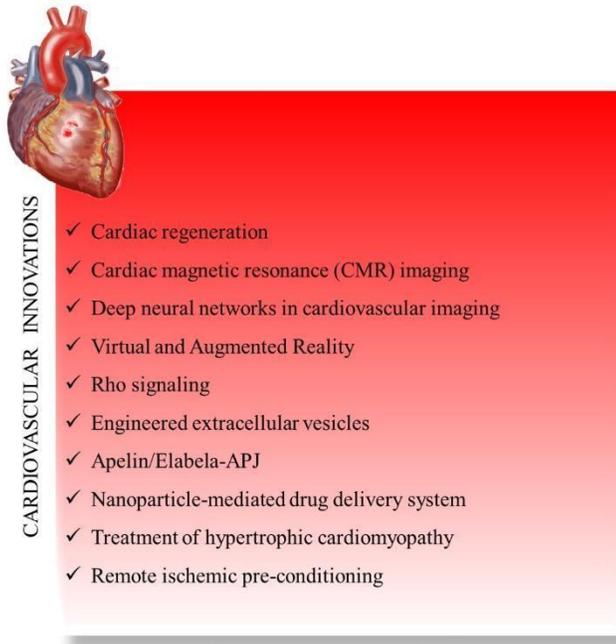


Figure 2. Important innovations in cardiovascular surgery

3.1. Cardiac Regeneration

Regenerative potential of the heart muscle is poor in mammals. This deficiency has been attributed to the lack of heart stem cells and obstacles that limit entrance of cardiomyocytes to the cell cycle for

division. Regeneration is a crucial field of research due to increasing incidence of heart failure and cardiac disease.

The innovation of stem cells and introduction of reprogramming technology have provided insight into regeneration (Tzahor and Poss 2017). It is important to understand the capacity of the heart for regeneration and controlling this capacity. Recent innovations on cardiac regeneration have been accomplished through stem cells and cardiomyocytes grown in the laboratory. Directed differentiation of embryonic stem cells with appropriate growth factors such as fibroblast growth factor (FGF) and bone morphogenetic protein 4 (BMP4) have enabled production of cardiomyocytes in large scales (Laflamme and Murry 2011). Human cardiomyocytes have been transplanted into rodents with induced ischemic injury and the results were promising with the improved cardiac function (Chong et al. 2014). Another innovative strategy to promote regeneration is to awaken the endogenous potential for the proliferation of cardiomyocytes and to replicate the regenerative process to repair cardiac damage as in neonatal mammals (Gabisonia et al. 2019). Promising innovations for cardiac regeneration include cyclin-dependent kinase (CDK) reactivating entrance of cardiomyocytes to cell cycle, exogenously administered proteins and microRNA with pro-proliferative activity (Wei et al. 2015; Bassat et al. 2017; Mohamed et al. 2018).

3.2. Cardiac Magnetic Resonance (CMR) Imaging

Cardiovascular magnetic resonance (CMR) imaging has increasingly become an essential tool in cardiology over the last two decades (Seetharam and Lerakis 2019). The generation of T1 and T2 mapping scanning have been facilitated by recent innovation in magnetic resonance scanning technology. Enhancement of cloud infrastructure has enabled increasing use of AI in cardiac imaging. In addition, CMR is considered the gold standard for non-invasive measurement of the left and right ventricular volumes and ejection fraction (EF) (Demirkiran et al. 2019).

Machine learning (ML), a subset of AI, has caused an evolution in cardiac imaging. Recently, the potential role of AI in improving CMR has been explored by many healthcare centers. In a study by Winther et al., a deep learning algorithm was successfully used for automated segmentation of the right and left ventricular epicardium in order to determine cardiac function (Winther et al. 2018). In a study by Tan et al., a deep learning approach was used for automated segmentation of the left ventricle in short-axis slices (Tan et al. 2017). In another study by Bai et al., a convolutional network was used to analyze CMR images automatically based on a large database of 93000 images to calculate the right and left ventricular volumes and mass in 5000 patients (Bai et al. 2018). CMR imaging will become much more effective in the future as technology continues to develop.

3.3. Deep Neural Networks in Cardiovascular Imaging

Deep Neural Networks (DNN) are an important form of machine learning. DNNs are promising modalities particularly for the transformation of diagnostic radiology techniques, including ECG, CT and MRI. Innovations in DNNs have enabled us to effectively use big data that are prevalent in the field of cardiovascular imaging. Using neural networks, deep learning algorithms have been produced to generate approximate cardiac measurements (Avendi et al. 2017).

Recently, DNNs have been used in order to detect subacute or chronic myocardial scars (Singh et al. 2018), to predict survival and underlying mechanisms of heart failure in the case of pulmonary hypertension (Dawes et al. 2017). DNNs have also been used to predict the risk for cardiovascular surgery and postoperative complications and mortality (Lippmann and Shahian 1997; Benedetto et al. 2020). DNNs are also valuable in congenital heart surgery, which has numerous complex combinations of diagnoses and procedures. In addition, DNN technique has been used for characterization of cardiac disease on ECHO. In a study by Ortiz et al., DNNs were used to predict 1-year mortality in patients with heart failure based on echocardiographic data (Ortiz et al. 1995). In another study by Mannil et al., DNNs were used to detect the presence of myocardial infarction on CT using texture analysis (Mannil et al. 2018).

3.4. Virtual and Augmented Reality (VR and AR)

Virtual and augmented reality can be defined as a 3D real world simulation that enables users to interact with it. VR provides 3D graphical output that is visualized with a wearable headset based on the integrated imaging data and input from users (Southworth et al. 2020). Dynamic anatomical nature of the cardiovascular system and permanent aim to decrease invasiveness make cardiovascular surgery a potential area of innovation for VR.

One of the greatest potential innovations in the future for VR in cardiovascular surgery is the shift from open sternotomy operations to minimal invasive procedures. Endoscopically and robot-assisted minimally invasive cardiac procedures have been developed due to increasing desire for reduced intraoperative trauma and shortened recovery period (Iribarne et al. 2011). Within this context, VR offers potential for improving visualization of surgical targets and enhancing the outcomes of beating-heart intracardiac surgery (Sadeghi et al. 2020). AR enables us to create interactive interfaces in order to make better preoperative planning, improved intraoperative navigation and training of surgeons. In a study by Ender et al., AR technology was used to assess optimal size of annuloplasty ring based on three-dimensional ECHO images of the annulus (Ender et al. 2008). Recent innovations, including VR and AR, in cardiovascular surgery have gained increasing interest in research in order to improve patients' quality of life, outcomes and to shorten the learning curve for young surgeons.

3.5. Rho Signaling

After the identification of Rho-kinase as an important effector of GTP-binding protein, crucial roles of Rho-kinase in the cardiovascular system have been demonstrated in numerous studies (Shimokawa et al. 2015). During the last few decades, considerable progress was recorded to gain insight in the therapeutic importance of Rho-kinase in the cardiovascular system. The inhibition of Rho-kinase has been shown to induce the development of arrhythmogenic right ventricular cardiomyopathy (Paterson et al. 1990). Rho-kinase plays a role in the pathogenesis of cardiovascular diseases by promoting vascular smooth muscle cells (VSMCs) and production of reactive oxygen species (ROS) (Zanin-Zhorov et al. 2017). It has been discovered that Rho-kinase is encoded by ROCK1 and ROCK2 genes (Leung et al. 1995). It has been proposed that ROCK2 may play an important role in cardiovascular homeostasis and cardiac diseases (Hansen et al. 2000). Studies have reported that ROCK1 and ROCK2 are involved in heart failure, cardiac hypertrophy, diabetic vasculopathy and fibrosis (Hartmann et al. 2015; Narumiya and Thumkeo 2018).

Therapeutic applications for Rho-kinase inhibitors are primarily involved in the area of cardiovascular diseases. Today, numerous pharmaceutical companies show a great interest in the Rho/Rho kinase signaling and Rho inhibitors (Akama et al. 2013).

3.6. Engineered extracellular vesicles

Functional improvement with cell therapies is yet to be fully understood, and therefore cell-free treatment methods through the release of extracellular vesicles (EVs), have drawn attention in recent years (Vagnozzi et al. 2020). Numerous studies in the literature have reported that EVs have a crucial role in many physiological and pathological conditions such as blood pressure, cardiac fibrosis, cardiomyocyte hypertrophy, apoptosis and regulation of angiogenesis (Beltrami et al. 2017). EVs have also been utilized as biomarkers of cardiovascular diseases (Jansen et al. 2017). In a study by Lai et al., therapeutic potential of EVs has been shown in protection of the heart from ischemic injury (Lai et al. 2010).

In recent years, several innovations have been made to modify native EVs, transforming them into engineered ones in order to improve their bioactivity in the cardiovascular system. For this purpose, EVs that have cardiac efficacy have been isolated from differentiated cell sources such as somatic cells, putative cardiac progenitor cells, and pluripotent cells (Agarwal et al. 2017). Significant progress has been made in the therapeutic effects of EVs in pre-clinical models of various cardiovascular diseases.

3.7. Apelin/Elabela-APJ

Apelin/Elabela-APJ signal is diffusely distributed within the cardiovascular system. This signal is involved in the regulation of vascular tension in adults and the development of heart and blood

vessels in fetuses. Apelin is involved in many physiological functions via its receptor APJ such as increasing myocardial contractility, vasodilatation and angiogenesis (Dray et al. 2008). More recently, an endogenous component of APJ, Elabela (ELA) has been discovered (Perjes et al. 2016). Apelin and ELA are highly expressed in the heart, suggesting that the apelin/ELA-APJ system may play an important role in cardiac function.

It has been reported that EPA/Apelin can be used in the treatment of preeclampsia (Liu et al. 2020). In an animal study by Ho et al., pregnant mice with induced ELA knockout exhibited symptoms of preeclampsia such as proteinuria and elevated blood tension that could be resolved by recombinant ELA infusion (Ho et al. 2017). Chronic administration of Apelin has been shown to reduce maternal hypertension and improve fetal growth (Inuzuka et al. 2013). Apelin is also a good protector against cardiac diseases such as myocardial infarction (MI). In a study by Zhang et al. Apelin-13 injection promoted myocardial angiogenesis, reduced cardiac fibrosis and size of MI and improved myocardial dysfunction in rats with induced coronary artery ligation (Zhang et al. 2014).

3.8. Nanoparticle-mediated drug delivery system

Certain diseases consist of diseased cells and molecules within healthy organs. Therefore, administration of medications has been a major strategy in contemporary medicine. In addition, drugs administered must overcome obstacles in circulating to cells, tissues, organs, reaching therapeutic targets. Innovations in medical nanotechnology

have led to the development of nanoparticle-mediated drug delivery systems (DDS). The introduction of nanoparticle-mediated DDS has modified the kinetics of the diagnostic and therapeutic agents. Drug targeting feature of these DDS enables utilization of physiological and pathophysiological properties specific to certain diseases, including atherosclerosis.

In a mouse model by Nakashiro et al., polymorphic poly(lactic-co-glycolic acid) (PLGA) nanoparticle injected directly to monocytes to intervene monocyte-induced inflammation in atherosclerosis, and it was found that delivery of PLGA to peripheral monocytes resulted in delivery to aortic macrophages, suggesting that intravenous PLGA nanoparticles gradually migrated to the atherosclerotic area two to seven days after the injection (Nakashiro et al. 2016).

Potential use of nanoparticle-mediated DDS in cardiovascular medicine include pulmonary hypertension, coronary stents, vein graft disease and myocardial ischemia-reperfusion injury. In addition, current contemporary nanoparticle technologies have been one of the promising approaches for myocardial repair (Awada et al. 2016).

3.9. Treatment of Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a genetic disorder of cardiac myocytes characterized by autosomal dominant sarcomeric gene mutation and is the most common monogenic cardiomyopathy. First line pharmacologic therapy includes the administration of β -blockers and non-dihydropyridine calcium-channel blockers.

Pharmaceutical innovations have resulted in the development of novel drugs for the treatment of HCM. Novel medications Mavacamten, a novel small oral molecule targets HCM mutations as an cardiac β -myosin modulator and leads to reversible inhibition of actin-myosin cross bridging (Anderson et al. 2018). In a mouse study by Green et al., mavacamten therapy attenuated HCM by suppression of hypertrophy and disarray of cardiomyocytes (Green et al. 2016). Perhexiline has been used as an oral inhibitor for antianginal treatment of HCM in Australia and New Zealand (Horowitz and Chirkov 2010). Ranolazine and eleclazine have been proposed to have beneficial effects on HCM through myocardial relaxation, arrhythmogenesis and ischemia (Olivotto et al. 2018). Besides medical therapy, some novel surgical techniques have been developed, including septal myectomy, mitral valve repair using an Alfieri stitch, apical myectomy with a transapical approach, using clips for transcatheter mitral valve repair and percutaneous intramyocardial septal RF (Radio Frequency) ablation (Crossen et al. 2016; Beaser et al. 2018).

3.10. Remote Ischemic Preconditioning

Remote ischemic preconditioning (RIPC) was described for the first time in 1993 by Przyklenk et al. and since then, several studies have reported that RIC through transient extremity ischemia reduces ischemia/reperfusion (IR) injury and protects vital organs including the heart and brain (Przyklenk et al. 1993; Mouton and Soar 2017). In RIPC, brief episodes of repeated IR are applied to a limb to induce remote protection of organs from potentially fatal IR injury (Chong JJ

et al. 2018). In a rat study by Costa et al., brief episodes of repeated IR applied to a limb increased antioxidant defenses in the heart and brain 10 minutes after the application of RIPC (Costa et al. 2016). According to experimental data, RIPC is a novel and inexpensive method that can be used to reduce perioperative ischemic complications (Kanoria et al. 2006). In a study by Ali et al. with 82 patients who underwent open abdominal aortic aneurysm repair, reduced troponin I levels and lower rates of postoperative myocardial injury were found in the groups administered RIPC through clamping of the common iliac artery for 10 minutes followed by reperfusion over 10 minutes (Ali et al. 2007). In addition, studies have stated that RIPC reduced major adverse cardiac and cerebrovascular events (MACCE) and myocardial injury when performed prior to coronary artery bypass grafting (CABG) operations (Yetgin et al. 2012; Payne et al. 2015).

CONCLUSION

Cardiovascular surgery is a field of medicine open to continuous innovations. Innovations in cardiovascular diseases aim to improve patient outcomes, efficiency of surgery, to increase success rate and survival, and to reduce complications, rate of mortality and treatment costs. Surgeons themselves are considered innovators due to the nature of their work. Most innovations in surgical techniques are based on modification and refinement of existing approaches. Research is ongoing about novel medical devices, techniques and medications. Rapid advancements in artificial intelligence,

nanotechnology, virtual and augmented reality, remote robotic surgery and tele-medicine will facilitate diagnosis, treatment and follow-up of cardiovascular diseases in near future.

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CHAPTER 6

NURSING MANAGEMENT OF COVID-19

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INTRODUCTION

Today, the COVID-19 pandemic is still continuing all over the world despite vaccination applications and partly owing to the new variants of the virus, (some of which are more potent such as the delta variant) (Kupferschmidt and Wadman 2021) and nurses among the other healthcare personnel are mostly affected by the disease as frontliners. Nurses have multidirectional duties in the management of COVID-19 ranging from self-protection against the risks, triage process and screening, to providing physical care and psychological support for the patients, recordings, reporting and being involved in scientific studies. This chapter begins with a brief update of the status and continues with COVID-19 burden on healthcare staff. Nursing management of COVID-19 is then discussed in detail.

1. UN UPDATE ON COVID-19

The novel coronavirus has invaded the world and resulted in an unexpected crisis worldwide. Many countries are under lockdown with hospitals converted to pandemic hospitals and shortage of beds, ICUs, medications has made the disaster further worse. Despite strict measures and vaccination programs implemented in many countries, Coronavirus Disease 2019 (COVID-19) continues its devastating effects worldwide. Moreover, new mutant variants of the novel coronavirus are emerging in different regions of the world with new features that pose challenges in fighting against the pandemic.

According to the World Health Organization's (WHO) daily situation report, there have been 177,108,695 confirmed cases and 3,840,223 deaths as of 18 June 2021. On the other hand, a total of 2,378,482,776 vaccine doses have been administered as of 16 June 2021 (WHO 1). Although the pandemic rate began to decrease in numerous regions, there is a far way to go for complete elimination of the disease.

2. COVID-19 BURDEN ON HEALTHCARE STAFF

The disease is affecting healthcare personnel directly as the frontliners dealing with patients who have confirmed or suspected COVID-19. Healthcare workers have responded to the challenge posed by COVID-19 devotedly. Everyday, in various regions of the world sensational media reports are released about mortality of healthcare staff from COVID-19, putting more stress on these personnel. Healthcare personnel and their families are at risk of transmitting the disease. The strict decision of quarantine and isolation from family in the case of suspected cases has increased psychological problems of healthcare workers (Kang et al. 2020). In a study by Wasim et al., depression was reported in 62.3%, anxiety in 63.7%, stress in 55.3% and insomnia in 53.3% of healthcare workers dealing with COVID-19 (Wasim et al. 2020).

The major sources of psychological problems among healthcare staff dealing with the pandemic include the risk of being infected by the virus, fatigue, burnout, disrupted sleep quality, increased work hours and putting their family members at risk of transmission (Patel et al.

2018). In addition, healthcare workers may experience fear due to contagious nature of the virus, unknown transmission routes and necessarily close contact with COVID-19 patients despite the protective measures (Moazzami et al. 2020). Moreover, mandatory use of personal protective equipment (PPE) increases nursing workload and burnout (Peng et al. 2020). Among healthcare personnel dealing with the pandemic, nurses have a specific place with multifaceted tasks they perform and critical roles in the management of the disease. In the next section of this chapter, nursing management of COVID-19 will be focused on.

3. NURSING MANAGEMENT OF COVID-19

Nurses are critical personnel who deliver healthcare services throughout the healthcare system. Their roles change in the hospitals and general population as needed and they adapt to new situations due to the nature of their job. During the COVID-19 outbreak, nurses are playing a central role in the frontline of the fight against COVID-19. In response to the pandemic, their roles change to care or respond to the needs of the patients, their caregivers and families (Sharma et al. 2020). The working hours of the nurses have been disrupted or prolonged during the pandemic.

Similarly to all other healthcare staff, nurses experience not only physical, but also emotional difficulties in such situations (Wu et al. 2009). In addition, studies have shown that these effects are not only short-term, but long-term impacts have also been observed (Maunder

et al. 2006). However, despite these negative impacts, nurses are working devotedly all over the world in the very center of the COVID-19. Nursing management of COVID-19 is multidirectional and covers a wide range of directions from screening and triage to physical care and psychological support for the patients and their families, management of limited sources of equipment and supplies, special care for children, elderly and pregnant women with suspected or confirmed COVID-19, critical care and even breaking bad news. These multidirectional roles of nurses in the management of COVID-19 are discussed below.

3.1. Self-protection against the risks

Staying safe comes first. Nurses first of all should take all necessary measures for protecting themselves, other healthcare staff and patients. Face to face contact with patients should be minimized as much as possible. According to WHO, observing breathing, hand hygiene and donning Personal Protective Equipment (PPE) are appropriate for the protection of healthcare personnel against COVID-19 (WHO 2). On the other hand, nurses should also show every effort to protect their family members, including isolation, if necessary (Jordan 2020). Since nurses work closely with patients due to their tasks, following hygiene rules and procedures becomes further important. Nurses have been subjected to exposure repeatedly to patients with varying viral loads (Samavedam 2021). Nosocomial infections have occurred in hospitals during the COVID-19 outbreak (Wang et al. 2020). Working continuously with PPE and donning

them twice a day have made working conditions for nurses difficult (Huang et al. 2020). Most importantly, healthcare organizations should have a procedure that permits nursing staff to raise any concern related to PPE policies and processes.

3.2. Screening for COVID-19

Nurses should be familiar with the latest scientific updates on COVID-19 as algorithms of disease management are changed and updated continuously due to the dynamic nature of the virus. All patients who arrive at the healthcare center are screened by nurses for symptoms of COVID-19. When screening for the infection, nurses should receive information from the patients about signs and symptoms of respiratory tract, recent travel history and exposure to someone with confirmed COVID-19 (Charles 2020) and record the data obtained. Based on this information, it is decided whether the patient should be tested for COVID-19.

3.3. Triage

Every healthcare organization has an established procedure for triage of patients with suspected or confirmed COVID-19. Triage procedures are mostly performed by nurses among the healthcare clerks or other personnel. The nurses should know these procedures well and follow-up the possible changes made in workflow. The role of nurses in triage of COVID-19 is not to diagnose the disease, but instead to identify and categorize the patients who should be tested and isolated from the other patients in the emergency department (Sharma et al.

2020). According to the triage, the nurse should refer the suspected cases to the isolation room, examination room or waiting room (WHO 3). Steps of a rapid and safe COVID-19 triage by nurses are shown in Figure 1.

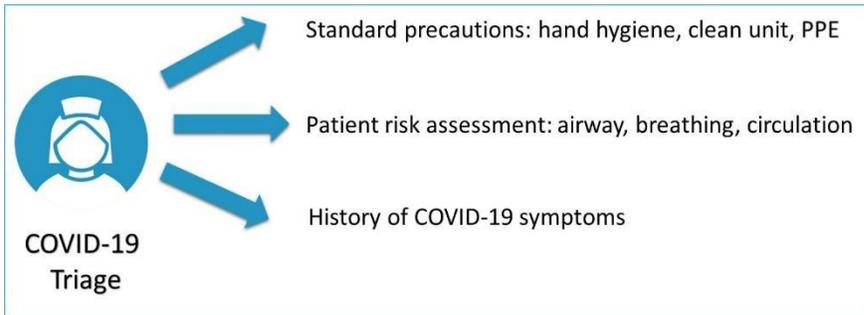


Figure 1. Principles of COVID-19 triage by nurses. ©Vacide Asik Ozdemir

During triage evaluation, patients with top priority should be sent directly to the isolation area without waiting. There must be a protocol for patients brought to the emergency department with an ambulance. In this case, EMS personnel should inform the triage personnel about the infected patients. Previous medical records of the patients should be accessed via the system electronically. Triage and isolation should be performed promptly in the patients with suspected symptoms of the COVID-19 (Schwartz et al. 2020).

3.4. Nursing Staff in Physical Care

Nurses have critical roles in physical care for patients within the scope of response to pandemic. Nurses helps patients to manage their physical needs and treat health conditions. For this reason, nurses

monitor and observe patients with COVID-19 to and to record any relevant information decision-making for. They deliver physical care during assessment, triage and quarantine of patients. Nurses perform these activities as soon as possible to quarantine the patients showing symptoms of COVID-19 or having positive test results in order to protect other patients that may not have the disease (Jordan 2020). Nurses identify patients with mild, moderate and severe symptoms they are involved in the management of the symptoms and monitoring the progression. In critical patients, they assist to the physician in crucial processes such as airway management and life support (Sharma et al. 2020). Nurses are able to see what is working and things that can be done for a more efficient management of COVID-19 patients.

3.5. Nursing Staff in Psychological Support

Nursing care for COVID-19 patients includes various psychological aspects that may cause stress disorder in the long term (Lehmann et al. 2015). Nurses provide psychological support for patients with COVID19 and their family members. They explain to the patients and families about the risks, management and progression of the disease. On the other hand, this risk of COVID-19 may cause psychological problems such as depression and anxiety for nurses. Nurses experience many stressors while working in the settings with high stress such as the COVID-19 pandemic. In addition, fear of being infected and transmitting the virus to their family members makes nursing care for these patients difficult (Maben and Bridges 2020).

3.6. Taking Care of Special Groups

3.6.1. Children with COVID-19

Although in the USA fewer cases of COVID-19 have been reported in children compared to adults (Stokes et al. 2020), the number of pediatric COVID-19 cases have been steadily increasing since March 2020. Pediatric nursing staff should take into account the child's clinical presentation, underlying medical conditions and the availability of home care when deciding whether the child needs inpatient treatment for COVID-19. Parents of these children are encouraged to follow the schedule of visits. Parents are instructed to find a way for coping if they have fear, emotional stress and depression about hospital visits for their children. Treatment of the disease in children is largely based on supportive care and management of the symptom. Supportive care should be provided for all children with COVID-19 (Chiotos et al. 2021). Nurses have crucial roles in the management of pediatric COVID-19 cases. When taking the medical history of the child, they ask the parents whether their child has been near someone with COVID-19 or in an area with lots of people having coronavirus. On the other hand, children with COVID-19 and critical respiratory distress usually require hospital admission.

3.6.2. Elderly with COVID-19

COVID-19 pandemic brings together a psychosocial burden on elderly people (Hantke and Gould 2020). Elderly people who are in isolation may exhibit nervous, stressful, agitated, angry behaviours during the

pandemic. Determining the need of care in older people is important for prevention of the COVID-19 disease and its complications and to make right decisions (Norman et al. 2020). Comprehensive evaluation of elderly patients with COVID-19 is the first step of the management, and these patients should be questioned especially about COVID-19-specific dyspnea, fatigue, cough, joint pain, drugs used, people contacted and caregivers (Polidori et al. 2020). Elderly should be taught how they can reduce the risks of infection. Family members or caregivers of these people should be encouraged about helping elderly patients to apply proper measures to avoid transmission (WHO 4). Nurses play an important role in fulfilling complex needs of elderly with COVID-19.

3.6.3.Pregnant Women with COVID-19

Nurses should be trained to provide obstetric care in pregnant women with suspected or confirmed COVID-19 infection. Before arrival of pregnant women to hospital, those with suspected or confirmed disease should be notified to the department of obstetrics in order to gain enough time to make the necessary preparations, identify the most important room for labour, to have all necessary PPE's at hand before arrivals of these patients (CDC). Pregnant women should be encouraged on that they will be able to receive all necessary care in the antenatal, postnatal and in case of abortion (WHO 5). All women admitted with confirmed COVID-19 infection in pregnancy should be recorded for future reference. In addition, given the possibility of decreased health care work and resources, new applications such as

telemedicine should be used as much as possible. Considerations in obstetric units about pregnant women with suspected or confirmed COVID-19 are shown in Figure 2.

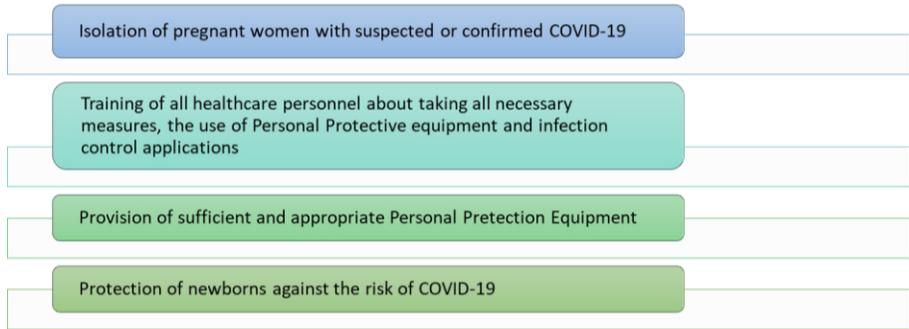


Figure 2. Considerations for the obstetric unit about management of pregnant women with suspected or confirmed COVID-19. ©Vacide Asik Ozdemir

3.7. Nursing Staff in Documenting and Reporting

Documentation and reporting are of critical importance in the health care systems. Nurses play a crucial role in both documentation and reporting, especially during crisis situations such as COVID-19 pandemic. Unlike routine records such as vital signs, daily medication, nurses should keep a record of entering and exit from isolation rooms regarding COVID-19 (Ye et al. 2020). They keep a record of all data about the patients including objective and subjective information and should provide accurate care. Current medical history should be received by nurses and should be updated. Documentation recorded by nurses should be:

- Accurate

- Complete
- Updated
- Well organized
- Confidential (for patients)

CONCLUSION

Nurses are at a very frontline in the fight with the novel coronavirus. They work in a very stressful environment and mostly in close contact with patients having COVID-19 due to their multifaceted tasks. Nurses, in the midst of pandemic provide triage, physical care and psychological support on one hand, while record and report medical information on the other hand, and also are involved in scientific research. Nursing staff should be psychologically and economically supported for their devoted working.

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CHAPTER 7

DETERMINATION OF SATISFACTION OF PATIENTS OVER 50 YEARS OF AGE WITH GENERAL HOSPITAL SERVICES IN THE SAMPLE OF 3RD STAGE UNIVERSITY HOSPITAL

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INTRODUCTION

Patient satisfaction is defined as an evaluation based on the fulfillment of expectations, either explicitly or implicitly. The fact that patient satisfaction assessments include direct patient perception and the results are effective in ensuring patient continuity has made research widespread (Afrashtehfar et al., 2020). Satisfaction studies are carried out in many areas such as determining satisfaction with disease-specific treatment methods, determining satisfaction with drug treatment, determining satisfaction with emergency services of hospitals, determining satisfaction with primary health care services, determining satisfaction with hospital services of inpatient or outpatient or two groups, determining satisfaction with doctors and determining satisfaction with nursing (Asamrew et al., 2020). Today, patient satisfaction is an issue that is given importance by institutions and institutions have publicly available evaluation results regarding patient satisfaction. It is argued that patient satisfaction is mediated by the patient's personal preferences and expectations, and the subjective reactions of the patient together with the treatment are also effective in satisfaction (Kraska et al., 2017). In patient satisfaction, it is determined how much the patients' own standards and values match with the service provided. Satisfaction is affected by the quality of the service received. If hospital services are below expectations; patient satisfaction is low, if the opposite is the case, it is high (Liu and Mao, 2019). Many factors such as the patients' values, culture and health status have impact on the patient's evaluation of the quality of the

services (Manzoor et al., 2019). Therefore, patient satisfaction relates to whether the patient actually receives quality care or whether they have positive treatment outcomes. In the process of improving the quality of hospital services, patient satisfaction is affected by many factors, as it is a concept that includes patient perception. In addition, General Operation and Physical Facilities of the Hospital, Nutrition Services, Discharge Procedures, Healthcare Professionals and Other Employees in the Hospital and trust in healthcare personnel play an important role on the patients' satisfaction as well as evaluation (Nguyen et al., 2020). In the literature; there are studies in which it is stated that the length of the waiting period related to the general procedures negatively affects the patient satisfaction, the satisfaction level of the patients with short general procedures is more positive than those with longer durations, and the satisfaction level is low due to the long waiting time (North et al., 2020). Liu and Mao (2019) in their study on hospital waiting time in China; It was seen that the patients perceived the actual waiting time related to general procedures longer than they experienced, and the total time they waited in the hospital was longer than the time they received health care. Due to the waiting time of the patients; it was seen that the satisfaction levels were low. In the study of Prakash (2010), it was stated that the short waiting period for the hospitalization procedures of the patients increased the level of satisfaction. In the study of Stamboglis and Jacobs (2020), in which all steps of hospital services were examined; it has been stated that the behavior of the employees during the hospital registration and discharge process, the waiting

time, the explanation of the procedures and procedures, and the cleanliness of the waiting areas are effective in satisfaction with the hospital services.

METHODS AND MATERIALS

The research was carried out in a descriptive way with the aim of investigating patients' satisfaction with general hospital services. The research was carried out in a descriptive way with the aim of investigating patients' satisfaction with general hospital services. The population of the study consisted of patients who applied to Kayseri Erciyes University Research and Application Hospital for different reasons. A total of 258 patients participated in the study, and consent forms were collected from the participants. The data obtained were evaluated in SPSS 23 package program. Mean, standard deviation, number, percentage, median and chi-square test, Kruskal Wallis and Mann-Whitney U test were used in the analyzes. In order to determine the usability of the satisfaction survey with hospital services in the research, Descriptive Information Form and Satisfaction with Hospital Services Questionnaire were applied. The descriptive form was developed to collect descriptive information about the patients included in the study. Form; It includes questions about age, gender, health insurance, educational status, previous hospitalization, how many days he has been in the hospital, previous hospitalization, how many times he has been hospitalized before, and the presence of a companion while in the hospital. Patient satisfaction form covers all stages from the patient's admission to the hospital until discharge.

When the literature is examined, it has been seen that specific questions should be asked in order to determine the level of patient satisfaction with hospital services.

In this direction, the Hospital Services Satisfaction Questionnaire was developed by the researchers in line with the literature in order to determine the satisfaction of the patients with the general hospital services. In the questionnaire, there are questions in which patients can express their views on the general operation and services of the hospital, the room they stay, the meals offered at the hospital, nurses, doctors, other health personnel, and other non-professional hospital staff. In this part of the questionnaire, the patients made their satisfaction evaluations as “I am very satisfied, satisfied, not satisfied”.

RESULTS

As presented in Table 1, the majority of the participants (71.7%) were the aged of between 50-65 years and male participants (78.2%). The almost equal number of the participants had primary and secondary level education while only 14.4% of the participants had tertiary level of education. The most of the participants (65.5%) were not smoking, as 91.8% of them were not using alcohol. The almost equal number of participants reported having a chronic disease and the majority of the participants (89.9%) reported to stay more than one time in this hospital.

Table 1. Socio-demographic characteristics of the participants

	n	%
Age		
50-65	185	71.7
Above 65	73	28.3
Gender		
Male	202	78.2
Female	56	21.8
Education		
Primary	109	42.2
Secondary	112	43.4
Tertiary	37	14.4
Smoking		
Yes	89	34.5
No	169	65.5
Chronic Illness		
Yes	134	51.9
No	124	48.1
Alcohol		
Yes	21	8.2
No	237	91.8
First time staying in this hospital		
Yes	26	10.1
No	232	89.9

Table 2 shows the answers given by the patients to the satisfaction survey with hospital services. The almost half of the participants are very satisfied with general operation and physical facilities of the hospital (48.4%) while 22.2% of the participants not satisfied with it. Nutrition services answers are varied among the participants; 37.2% of them are very satisfied, 34.1% of them are satisfied and 28.7% of

them are not satisfied. The answers of discharge procedure among the participants are varied; 26.7% of them are very satisfied, 39.5% of them are satisfied and 33.8% of them are not satisfied. The majority of the participants reported (38.7%) not satisfied for healthcare professionals and other employees in the hospital. Lastly, the most of the participants showed (81.3%) trust in healthcare professionals.

Table 2. Distribution of the answers given by the patients to the satisfaction survey with hospital services

(n=258)	very satisfied (n %)	satisfied (n %)	not satisfied (n %)
General Operation and Physical Facilities of the Hospital	125 (48.4)	76 (29.4)	57 (22.2)
Nutrition Services	96 (37.2)	88 (34.1)	74 (28.7)
Discharge Procedure	69 (26.7)	102 (39.5)	87 (33.8)
Healthcare Professionals and Other Employees in the Hospital	63 (24.5)	95 (36.8)	100 (38.7)
Trust in Healthcare Personnel	78 (30.2)	132 (51.1)	48 (18.7)

The mean score of the visual scale used to determine the satisfaction of the patients with the hospital service is 23.13 ± 2.46 . A weak, positive and statistically significant relationship was found between the satisfaction of the patients with the hospital service and their trust in the healthcare staff ($r = 0.322$, $p = 0.000$) (Table 3).

Table 3. Visual scale mean score for patients' satisfaction with hospital services

The scale of trust for healthcare professionals		
	r	p
Visual scale for patients' satisfaction with hospital services	0.322	0.000

Table.3 shows some descriptive characteristics of the patients and the distribution of visual scale scores for their satisfaction with hospital services. According to the results of the Kruskal gamma test, there is no statistically significant relationship between the ages of the patients and the median scores they give to hospital services ($p=0.577$), gender and the median scores of the hospital services ($p=0.324$), education and the median scores of the hospital services ($p=0.206$), smoking and the median scores of the hospital services ($p=0.654$), alcohol and the median scores of the hospital services ($p=0.285$) and first time staying in this hospital and the median scores of the hospital services ($p=0.285$). However, there is a statistically significant relationship found between chronic illness and the median scores of the hospital services ($p=0.001$).

Table 4. Comparison of patients' descriptive characteristics and visual scale scores for their satisfaction with hospital services

Age	Median	Min-max	Kruskall Gamma	P value
50-65	8.00 (3.00)	4.00 - 10.00	0.094	0.577
Above 65	9.00 (2.00)	3.00 -10.00		
Gender				
Male	8.00 (2.00)	1.00 - 10.00	0.433	0.324
Female	7.00 (2.00)	3.00 -10.00		
Education				
Primary	9.00 (3.00)	5.00-10.00	0.621	0.206
Secondary	8.00 (2.00)	1.00-10.00		
Tertiary	7.00 (2.00)	2.00 -10.00		
Smoking				
Yes	8.00 (2.00)	1.00 -10.00	0.056	0.654
No	8.00 (2.00)	4.00 -10.00		
Chronic Illness				
Yes	9.00 (3.00)	2.00 -10.00	0.348	0.001
No	8.00 (2.00)	1.00 - 10.00		
Alcohol				
Yes	8.00 (3.00)	6.00-10.00	0.643	0.285
No	7.00 (2.00)	4.00 - 10.00		
First time staying in this hospital				
Yes	9.00 (3.00)	2.00 -10.00	0.481	0.472
No	8.00 (2.00)	6.00-10.00		

P<0.05 values are statistically significant; a statistically significant difference was found in chronic diseases.

DISCUSSION

In this study, in which patients' satisfaction with general hospital services was investigated, 92.1% of the patients stated that they would prefer and recommend this hospital again. The mean score of the visual scale used to determine the satisfaction of the patients with the hospital service is 23.13 ± 2.46 . A weak, positive and statistically significant relationship was found between the satisfaction of the patients with the hospital service and their trust in the healthcare staff ($r = 0.322$, $p = 0.000$). When the answers given by the patients regarding their satisfaction with the general hospital services are examined, it is seen that the answers are generally 'very satisfied and satisfied'. More than a quarter of the patients answered the open-ended question about the dissatisfaction in hospital services; more than a quarter of room conditions (cleanliness, number of patients, attendant conditions); stated that toilets (number, location, cleanliness, lack of toilet paper) created dissatisfaction. For the satisfaction of the patients with the hospital services, the physical characteristics of the hospital, social facilities, rather than the food services; it was found that the satisfaction statements for the hospital staff were more positive. In the literature, it is seen that the satisfaction with hospital services is more positive, especially for doctors and nurses. In particular, it is seen that the satisfaction levels of healthcare professionals are higher (Xiong et al., 2018). The results are consistent with our findings.

In this study, the physical characteristics of the hospital, its social facilities, rather than the food services, for the satisfaction of the patients with the hospital services; it is seen that the satisfaction reports for the hospital staff are more positive. It is thought that the patient satisfaction with general hospital services is especially influenced by the doctor and the nurses' performance. In the literature, it is seen that especially doctors and nurses affect satisfaction with hospital services (Trinh et al., 2019). The results are consistent with our findings. In our study, it was found that more than half of the patients were "satisfied" with their discharge procedures. It is possible to say that monitoring the discharge process of the patients and establishing a standard in the institution will increase patient satisfaction. The high level of patient satisfaction may be due to the low expectations of the patients regarding health services, depending on the average age of the patients. The findings obtained from our study; the level of satisfaction with hospital services was found to be high. According to the study of Sparkes (2019); patients who stay in the hospital longer have enough time to trust the nurse. In our this study; it is possible that the higher confidence of the patients hospitalized for a long time is related to the fact that the patients spend more time with the nurses and are satisfied with their nursing care. It is seen that the satisfaction level of the patients with the general hospital services is high.

CONCLUSION

According to the results of the study; it is seen that trust in the nurse has an effect on satisfaction with hospital services. It can be said that the nurses' attempts to develop trust in the patient-nurse relationship will improve satisfaction with hospital services. However, the results obtained from this study cannot be generalized as they include the responses of the patients in the hospital where the research was conducted.

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