Letter from the Editor-in-Chief

Dear Colleagues,

This is the second letter from editor-in-chief of the second issue of *The Egyptian Journal of Hypertension and Cardiovascular Risk*. While there are already several periodicals of high standards in the field of cardiovascular medicine in Egypt, I hope that our journal will find its place in promoting research and innovation for our community.

Starting with the next volume, we intended to make some significant changes. As I told you before, We've decided to meet the standards set out by the “Uniform Requirements for Manuscripts Submitted to Biomedical Journals" developed by the International Committee of Medical Journal Editors (http://www.icmje.org), and have refined our Author Guidelines accordingly. For more information on submitting a paper, please visit the journal's instruction to authors.

We contacted the Egyptian Knowledge Bank (EKB) to be responsible for publishing our journal. Some paper work is mandatory for accomplishing this process. The EKB asked for some important details like the journal strategic plans, the editorial board, the frequency of publications, type of articles accepted, peer reviewing, .. etc. Actually, we are in great hurry to finalize all the requirements to start our new issues of the new electronic format system.

On reaching this milestone, I will proudly encourage you all to submit your work for consideration for publication in *The Egyptian Journal of Hypertension and Cardiovascular Risk*.

Sincerely,

Azza Farrag, MD, FESC
Professor of Cardiovascular Medicine
Cairo University
Editor in Chief

President Massage

Towards an Ideal Antihypertensive Drug

M. Mohsen Ibrahim, MD

Prof. of Cardiology - Cairo University and President of the Egyptian Hypertension Society

Once diagnosed established essential hypertension (HTN) mandates a lifelong drug therapy since there is no permanent cure from established essential HTN. Pharmacologic therapy in addition to its cost carries the risks of side effects, failure to target the presser mechanisms, prevent progression of target organ damage and address associated CV risk factors commonly present in hypertensive patients. Therefore, an ideal antihypertensive drug should be affordable, orally effective in lowering BP, capable of preventing and regressing target organ damage, free from side effects and can address other associated CV risk factors. The choice of one drug over another should ideally be supported by good clinical evidence. The therapeutic effect of the drug is expected to be maintained throughout the 24 hours dosing interval. A longer half-life is a therapeutic advantage which can cover the early manning risk of BP when acute hypertensive life-threatening complications occur.

Inflammation might contribute to the development of HTN and its complication. Antihypertensive drugs with anti-inflammatory potential provide a definite advantage. Lowering of markers of inflammation was reported with some antihypertensive medications. Inflammation plays a central role in the development of atherosclerotic lesions and CV events. Drugs that lower markers of inflammation in hypertensive patients will help in prevention and regression of atherosclerotic lesions.

Endothelial dysfunction is an early event in vascular pathophysiology and is implicated in HTN and atherosclerosis. An ideal antihypertensive will have beneficial effects on endothelial function. Reduction in arterial stiffness which is common in elderly hypertensive patients is a pre-requisite for an ideal antihypertensive drug.

Prevention and regression of hypertensive complications namely LV hypertrophy, atherosclerosis and renal dysfunction are mandatory for an ideal antihypertensive drug. LV hypertrophy in hypertensive patients significantly increases the risks of coronary heart disease, stroke arrhythmias and heart failure. Reduction in LV mass and left atrial size can prevent or delay the recurrence of atrial fibrillation and HF. Prevention and regression of LV hypertrophy are important targets of therapy.

Insulin resistance and diabetes are common among hypertensive patients. An ideal drug will improve insulin resistance and help prevent diabetes. On the other hand lowering of glomerular pressure will prevent progression of diabetic nephropathy and prevent the decrease in glomerular filtration rate (GFR) in patients with micro or macro albuminuria.

It is expected that an ideal agent will not only effectively lower BP but can improve glucose and lipid metabolism and regress inflammatory markers and target organ damage.

The new ESH guidelines for management of hypertension 2023 A small tour at the large city

Haytham Soliman, MD

Fayoum University

In 22nd of May 2023 the European society of hypertension issued a new guideline for management of arterial hypertension that contained a lot of new concepts and updated strategies

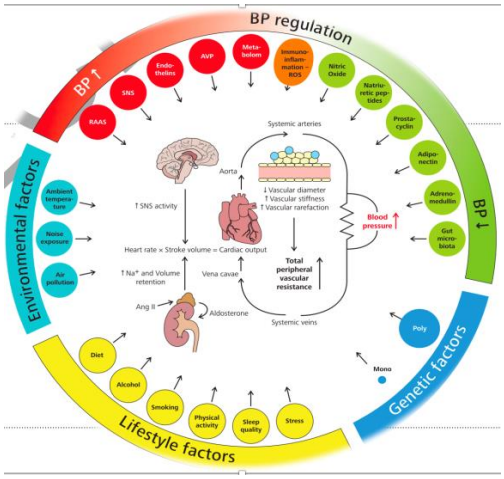
It is practically impossible to gather all these new information in one article so we will try to highlight the most important and innovative topics as much as we can.

The first thing that we notice in these guidelines is the concept of globalization of the factors affecting that hypertensive patient taking into consideration the risk factors the ethnicity of the patients the genetic factors, the lifestyle changes and the other comorbidities of the patient and this concept is extremely obvious in this diagram presented by these guidelines.

Another clear recommendation of the guidelines is to combine the stage of hypertension with the presence of risk factors or target organ damage to determine the proper management of this patient according to his risk category and not only their blood pressure values measured for these patients.

Definition of BP categories, hypertension grades and stages according to office BP

Recommendations and statements	CoR	LoE
It is recommended that BP is classified as optimal, normal, high normal, or grade 1, 2 or 3 hypertension, according to office BP.	I	C
In addition to grades of hypertension, which are based on BP values, it is recommended to distinguish stage 1, 2, and 3 hypertension. Stage 1: Uncomplicated hypertension without HMOD, diabetes, CVD and without CKD ≥ stage 3 Stage 2: Presence of HMOD, diabetes, or CKD stage 3 Stage 3: Presence of CVD or CKD stage 4 or 5	I	C



Choice of blood pressure measuring devices

Choice of blood pressure measuring devices is another important point addressed by the guidelines. Although the mercury device is accurate as stated by the guidelines, it's replaced by the aneroid device, the digital inflatable devices with a list of the accurate devices that we can use. The guidelines stated clearly that the cuffless digital devices are not recognized as accurate devices for measuring or even following up blood pressure till this moment.

Home blood pressure measurement

Home blood pressure measurement is taking a lot more interest and important role in diagnosing and following up blood pressure and if the patient is well trained this can replace some of the indication of ambulatory blood pressure now and in the future.

In the quest off discovering hypertensive patients and prevent the complication of hypertension as early as we can it's

recommended now to measure the blood pressure to children above three years of age and if this children autumn born to hypertensive parents, they have congenital heart disease that may increase blood pressure, or any congenital anomaly that may cause secondary hypertension it's now recommended in the guidelines to measure their blood pressure even earlier than three years of age.

Classification of hypertension

One of the new things in the guidelines is introducing one more category of hypertensive patients which are patients with isolated diastolic hypertension meaning that these patients have a systolic blood pressure less than 140 mmHg and diastolic blood pressure over 90 mmHg. These are often young male patients with obesity, diabetes, smoking and although they are not represented in the trials because they represent 7% of the hypertensive population but these patients are at risk, and they should receive treatment for diastolic hypertension.

We all know that treating elderly patients above 80 years of age is challenging and all that recommendation is to start low and go slow but in this guidelines there are combination of age risk factors and frailty with highlighting the cognitive functions of the elderly patients to choose your strategy in treating patients above 80 years of age so this is the first time to include the frailty index into the evaluation of elderly patients to manage them properly.

Classification of office BP

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and	80–84
High-normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension[a]	≥140	and	<90
Isolated diastolic hypertension[a]	<140	and	≥90

The BP category is defined by the highest level of BP, whether systolic or diastolic.
[a]Isolated systolic or diastolic hypertension is graded 1, 2 or 3 according to SBP and DBP values in the ranges indicated. The same classification is used for adolescents ≥16 years old (Section 15.1).

BP-lowering strategies in patients older than 80 years

Characteristics	Group 1 Fit	Group 2 Slowed but autonomous for most activities	Group 3 Severely dependent
Diagnosis	-ADL (Katz) ≥5/6 and -absence of clinically significant dementia (MMSE≤20/30) and -routine walking activities	-Profile between Groups 1 and 3	-ADL (Katz) ≤2/6 or -severe dementia or -(MMSE ≤10/30), chronic bedridden or -end of life
Therapeutic strategy	- As recommended below	-Individualize treatment	-Individualize treatment -Prioritize therapeutic strategies according to comorbidities and polypharmacy issues

Katz Index of Independence in Activities of Daily Living (ADL) is a scale rated from 0 (completely dependent) to 6 (completely autonomous). This scale comprises 6 ADL: Bathing, Dressing, Toileting, Transferring, Feeding and Continence. For each ADL, '0' means that the person is unable to do it without assistance, 0.5 need of some assistance, 1 no need of any assistance [970]. MMSE, Mini mental status evaluation.

Criteria to define HMOD

Measurement	Parameter	Abnormality threshold
ECG		
LVH	$S_{V1} + R_{V5}$ (Sokolow–Lyon)	>35 mm
	R wave aVL	≥11 mm
	$S_{V3} + R_{aVL}$ (Cornell voltage)	>28 mm (M), >20 mm (W)
LVH	Cornell voltage (+6 mm in W) × QRS duration (Cornell duration product)	>2440 mm s
ECHO		
LVH	LVM/BSA (g/m^2)	>115 (M), >95 (W)
	LVM/height ($g/m^{2.7}$)	>50 (M), >47 (W)
RWT	LV conc. Remodeling	≥0.43
LV chamber size	LVDDim/height	>3.4 (M), >3.3 (W) cm/m
LV diastolic dysfunction	*e′* velocity septal	<7 cm/s
	e′ velocity lateral	<10 cm/s
LV filling pressure	*E*/*e′* average ratio	>14
	LAV/BSA	>34 ml/m^2
	LAV/$height^2$	>18.5 (M) or >16.5 (W) ml/m^2
LV systolic dysfunction	GLS	<20%
Kidney		
Function	eGFR	<60 ml/min/1.73 m^2
Albuminuria	UACR	>30 mg/g
Renal resistance index	RRI	<0.07
RRI ?		
Large artery stiffness		
Pulse pressure	Brachial PP (>60 years)	≥60 mmHg
Pulse wave velocity	baPWV (in people 60–70 years)	>18 m/s
	cfPWV (in people 50–60 years)	>10 m/s
Carotid atherosclerosis		
	Plaque	IMT ≥1.5 mm, or focal increase in thickness ≥0.5 mm, or 50% of surrounding IMT
	IMT	>0.9 mm
Coronary atherosclerosis		
	CAC	Age-specific and sex-specific reference value
LEAD		
	ABI	<0.9
Eye		
	KWB score	Grade III (hemorrhages, microaneurysms, hard exudates and cotton wool spots) and grade IV (papilloedema and/or macula edema)
Microvascular changes	Wall-to-lumen ratio	no established reference value

Hypertensive mediated organ damage is extremely challenging and it's very important to know this complication in assessing the risk off of this patient and to modify the treatment plan. These guidelines highlighted a more detailed workup to discover the presence of hypertension mediated organ damage in order to treat them properly.

Secondary hypertension

Secondary hypertension could be challenging in both the diagnosis and management these guidelines offered a clear and simplified diagrams to help suspecting that secondary cause of hypertension according to age, to illicit the most common clinical findings in every second because of hypertension, and to propose the plan of management of these patients.

Hypertension in Cancer patients

We all know that cancer survivors are increasing due to the improvement of diagnosis and treatment, but this anti-cancer treatment comes with its complications. One of the most important side effects of cancer treatment is hypertension and the guidelines is stating clearly the type of cancer anti-cancer treatments and its effect on blood pressure so if you're treating a hypertensive patient with cancer or a history of cancer you should revise his anti-cancer treatment to see whether it's causing the elevation of blood pressure or not.

Challenging scenarios

Many clinical scenarios are challenging in managing hypertensive patients include acute stroke or patient with CKD, the new guidelines is providing us with illustrative diagrams to help us treating patients with acute stroke and managing CKD patients with proper treatment according to the stage of their illness. One of the most important points is the use of RAAS blockades in managing patients with CKD even in stage four or five not requiring hemodialysis.

Treatment of hypertension

There were no drastic changes concerning treatment, treatment combinations, the targets of blood pressure in every category or the use of beta blocker as a first choice of therapy in compelling indications. The new concept of quadric-pills or poorly pills is addressed clearly in these guidelines, trying to combine the different groups of medication into one pill of medication to increase the adherence of the patients to treatment.

Hypertension induced by selected anticancer treatments

Drug class	Selected example drugs	Selected malignancies	Potential mechanisms	Hypertension incidences	Comments
VEGF inhibitors	Axitinib, Bevacizumab, Cabozantinib, Dasatinib, Lenvatinib, Nilotinib, Pazopanib, Ponatinib, Ramucirumab, Regorafenib, Sorafenib, Sunitinib, Tivozanib, Vandetanib	Renal, hepatocellular, thyroid, gastrointestinal stromal cancer	↑Endothelin-1 bioavailability ↓ NO bioavailability Oxidative stress Endothelial dysfunction Microvascular rarefication ↓Lymphangiogenesis Kidney injury	**20%-90%**	
Bruton TK inhibitors	Acalabrutinib, Ibrutinib	Chronic lymphocytic leukemia, mantle cell lymphoma	↓Heat shock protein ↓NO bioavailability	**71%**	Long-term effects
Platinum-based compounds	Carboplatin, Cisplatin, Oxaliplatin	Mesothelioma, testicular, bladder, gynaecological, colorectal, and lung cancers	↓NO bioavailability Endothelial dysfunction Kidney injury	**53%**	Long-term effects
Alkylating compounds	Busulfan, Cyclophosphamide, Ifosfamide	Haematologic and solid organ malignancies	↓VEGF bioavailability and vascular/kidney toxicity (Cyclophosphomide)	**36% in adults 15%-58% in children**	Possible confounding by concomitant use of glucocorticoids; long-term effects
Calcineurin inhbitors	Cyclosporin, Tacrolimus	After stem cell transplantation	↑Vasoconstriction (↑RAS and Endothelin-1) ↓NO bioavailability ↑SNS	**30%–60%**	Long-term effects
Proteasome inhibitors	Bortezomib, Carfilzomib	Multiple myeloma	↓NO bioavailability Endothelial dysfunction	**10%-32%**	
BRAF/MEK inhibitors	Binimetinib, Cobimetinib, Dabrafenib, Encorafenib, Trametinib, Vemurafenib	Melanoma, colorectal cancer	CD47 upregulation ↓cGMP, ↓NO Endothelial dysfunction	**19.5%**	
RET kinase inhibitors	Pralsetinib, Selparcatinib, Vandetanib	Thyroid, non–small cell lung cancer	CD47 upregulation ↓cGMP, ↓NO Endothelial dysfunction	**21%-43%**	
PARP inhibitors	Niraparib, Olaparib[a]	Breast, ovarian cancer	Inhibition of dopamine, norepinephrine, and serotonin re-uptake	**19%**	
mTOR inhibitors	Everolimus, Sirolimus	Renal cell, breast, PNET cancer	↓VEGF bioavailability	**No data**	
Androgen synthesis inhibitors	Abiraterone	Metastatic prostate cancer Prostate cancer	Mineralocorticoid activity of accumulated steroid precursors	**26%**	
Androgen receptor blockers	Enzalutamide	Metastatic prostate cancer	Unknown	**11%**	

Other issues to be addressed

Of course, there are no guidelines that do not address the value of lifestyle modification in treating any disease and in hypertension guidelines the value with no major changes in these recommendations.

For the resistant patient to medical treatment the guidelines are addressing nonpharmacological treatment for hypertensive patients. The renal denervation is back with solid indication according to the results of the simplicity 4 trial that proving effectiveness of this line of treatment in selected cases.

In the future as mentioned by the guidelines there will be more intervention options for resistant hypertensive patients including a calculated arterial venous fistula, the carotid sinus stimulating device and the MODERATO system that change the AV conduction throughout a pacemaker mechanism to decrease the preload and improve the blood pressure.

The last concept is the telemedicine which is highlighted by the guidelines as a convenient way to follow up your patient or to screen the patients with hypertension complication and to modify the risk category of your patient according to any new risk factors that could happen during treatment but of course it's not recommended as the first tool to diagnose or to evaluate a new hypertensive patient.

Use of renal denervation

Recommendations and statements	CoR	LoE
RDN can be considered as a treatment option in patients an eGFR >40 ml/min/1.73m^2 who have uncontrolled BP despite the use of antihypertensive drug combination therapy, or if drug treatment elicits serious side effects and poor quality of life.	II	B
RDN can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 ml/min/1.73m^2.	II	B
Selection of patients to whom RDN is offered should be done in a shared decision-making process after objective and complete patient's information.	I	C
Renal denervation should only be performed in experienced specialized centers to guarantee appropriate selection of eligible patients and completeness of the denervation procedure.	I	C

Mini Review

Role of Exercise in the Management of Type 2 Diabetes Mellitus

Amr Abdel Aal, MD
Helwan University

Background

Diabetes Mellitus (DM) is chronic metabolic disorder representing a major health problem and economic burden facing both developed and developing countries. The main characteristic metabolic abnormality of DM is lifelong hyperglycemia associated with carbohydrate, lipids and protein impaired metabolism resulting in life threating long term complications affecting major body organs as the heart and kidney. Type 2 DM (T2DM) accounts for 90-95% of all diabetic cases with estimated prevalence of 266 million people worldwide in 2011 with expected surge to affect 552 million people by 2030 [(1)]. Routine physical exercise has been considered as a cornerstone in the management of T2DM owing to its proved efficacy in reducing glycemia in addition to reduction of diabetes related complications [(2)].

Exercise effect on T2DM

- **Prevention of DM**

Regular physical exercise plays a crucial role in the prevention of T2DM through improvement of insulin sensitivity [(3)], change in both body mass and composition and ameliorating hemostatic metabolism [(4)]. Participation in leisure-time physical activity of moderate to high intensity was associated with 65% less chance of developing DM in prediabetic patients after 4 years follow-up [(5)].

- **Insulin resistance (IR)**

The uptake of glucose by skeletal muscles from the bloodstream is done through mechanisms dependent on glucose transporter type 4 (GLUT4), the translocation of which to the muscle membrane in the resting state relies on the presence of insulin. IR is characterized by decreased expression of GLUT4 protein in muscles. Regular physical exercise improves GLUT4 translocation through insulin independent pathway which enhances the ability of skeletal muscles to improve glucose uptake and transportation [(2)].

- **Pancreatic islets ß cell function**

T2DM associated hyperglycemia and hyperlipidemia lead to toxic effect on pancreatic ß cell causing impairment of its function. Regular physical exercise is associated with gradual consumption of accumulated glucose and lipids reversing their toxic effect on pancreatic ß cell thus promoting recovery of injured islets function and protecting residual ß cells which help the pancreas to maintain or even improve its endocrine function [(2)].

- **Insulin sensitivity**

Physical exercise facilitates the physiological effect of insulin as resistance exercise is associated with increase in strength and cross-sectional area of skeletal muscles which results

in increase of insulin receptor numbers and thus improvement of insulin sensitivity [2].

- **Susceptibility genes**

Obesity associated insulin resistance is a key player in the pathogenesis of T2DM. Physical activity has a positive impact on high genetic risk subgroups against obesity through its ability to attenuate the impact of obesity-predisposing gene variants like FTO on body mass index or body adiposity index in various age groups [6]. The effect of physical exercise on susceptibility genes can be explained by modulation of DNA methylation which is believed to be a potential epigenetic mechanism defining the interaction between genetic variants and lifestyle changes [2].

Effect of various exercise regimen on T2DM

- **Aerobic exercise**

Regular aerobic exercise training in T2DM is associated with improvement of blood glucose levels, HbA1C and insulin sensitivity. In addition, it may halt diabetes associated complications such as CVD, nephropathy, and dyslipidemia. Aerobic exercise causes 5 folds acute increase of skeletal muscle glucose uptake by insulin independent mechanisms which may be maintained up to 2 hours by insulin-independent mechanisms and up 48 hours by insulin dependent mechanisms post exercise if exercise is prolonged [4].

- **Resistance exercise**

There is no consensus on the effect of regular resistance training on improvement of glycemic abnormalities in T2DM with contradictory outcome from several clinical trials. However, resistance exercise training is associated with considerable **i**mprovement in strength, bone mineral density, blood pressure, lipid profiles, skeletal muscle mass, and insulin sensitivity [7].

- **Combined**

The greatest benefit from exercise is gained from combined exercise training when compared to either form alone. Combined training is associated with better improvement of insulin sensitivity than that achieved by aerobic exercise only. Combined training results in increased muscle mass, better glycemic control, higher fatty acid oxidation capacity, physical function, and mental health [4].

Exercise Recommendations for T2DM

The American Diabetes Association recommends that patients with T2DM should follow moderate -to- high-intensity aerobic exercise for 150 min or more/week in at least 3 sessions/ week. It also recommends 2-3 sessions/ week of resistance training on non-consecutive days. Exercise intensity should be tailored for each patient depending on his disease level, health condition, and individual fitness evaluation [7].

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Original research

Higher Rates of Thrombolysis Failure and Stent Thrombosis During the COVID-19 Upsurges: What Should We Learn for Recurrent Waves?

*Ahmad Samir, MD[1,2]; Michael Gergis, MD[2]; Ahmed Elborae, MScError! Bookmark not defined.,[1]; Kerolos W agdy, MSc[2]; Ahmed Hassan, MD**Error! Bookmark not defined.**,[1]; Hesham Bahaa, MD[2]; Mohammed Hosny, MD**Error! Bookmark not defined.**,[1]; Ahmed ElGuindy, MD[2,3]

Abstract

Background: On-site thrombolysis as an alternative to transfer for primary PCI (pPCI) was utilized during COVID-19 first peak in many localities enforced by the overwhelming burden on the unprepared health systems. However, higher rates of thrombolysis failure, and excess of STEMIs secondary to stent thrombosis were frequently reported during COVID-19 first peak, questioning a potential linkage to SARS-CoV-2-related prothrombotic status. The recent alarming spread by the new emerging SARS-CoV-2 variants in many regions threatens low- and middle-income countries by overwhelming crises similar to the commencement of the pandemic. In this retrospective analysis, we contrasted the clinical profiles, revascularization strategies and outcomes of STEMI patients presenting to our system during the first COVID-19 surge (n=37), to STEMI presentations in the same interval of the previous year (n=77), to inspect the impact of COVID-19 on STEMI presentations and outcomes.

Results: Patients' profiles were mostly comparable between the COVID-19-era- and the control- groups. Compared to the controls, STEMI patients during the COVID-19-era had significantly higher rates of thrombolysis failure (5 (63%) vs 3 (21%), p = 0.05) and of STEMIs due to stent thrombosis (5 (16%) vs 2 (3%), p = 0.01).

Conclusions: A prevalent prothrombotic milieu parallels SARS-CoV-2 upsurges, disproportionately exceeding numbers of confirmed SARS-CoV-2 infections. This prothrombotic status probably enhanced stent thrombosis and reduced success of thrombolysis in STEMI cohorts. It is prudent to consider these observations in the unluckily event we faced recurrent upsurges dominated by the emerging SARS-CoV-2 variants.

Keywords: COVID-19, STEMI, thrombolysis, stent thrombosis, Egypt

1, Faculty of Medicine, Cairo University, Cairo, Egypt, 2, Aswan Heart Centre, Aswan, Egypt. 3, National Heart and Lung Institute, Imperial College London – UK

***Corresponding author:** Ahmad Samir, MD.

Telephone: +20 100 264 7275, ***Email address***: Ahmadsamir11@cu.edu.eg, ***ORCID***: 0000-0003-4401-4976, ***Address***: Faculty of Medicine, **Cairo University, Egypt** (postal code: **12613)**

Background

Since the World Health Organization (WHO) declared the coronavirus 2019 disease (COVID-19) as a pandemic in March 2020,[1] there was an astonishing impact on ST-segment elevation myocardial infarction (STEMI) presentations and outcomes.[2–6]

Despite the reduced numbers of presentations observed in the beginning of the pandemic, STEMIs during the COVID-19 first peak were characterized by substantially worse prognosis and higher in-hospital mortality than usual.[2,7,8] Such observation was initially attributed to the common fears of contracting SARS-CoV-2 infections at healthcare facilities, suggesting that only sicker STEMI patients selectively presented (and very late) to medical services.[9] Nevertheless, alarming signals for increased thrombogenicity accompanying the COVID-19 syndrome started to be a big concern, with a possible worsening impact on STEMI presentations and prognosis.[10]

On the other hand, many health systems, particularly in low- and middle-income countries, were unprepared for the overwhelming burdens of such crisis, and were enforced to implement resilient plans with many unstudied compromises. Prominent among these was appraising thrombolysis as an alternative reperfusion strategy for STEMIs, aiming to minimize patient transfer between facilities and reduce exhaustion of medical resources.

Emergence of the new and highly infective SARS-CoV-2 variants resulted in devastating spreads, that surpassed all preparations in many countries and resulted in recurrent crises, similar to what was met in the beginning of the COVID-19 pandemic, or even worse.[11]

Thereby, we opted to explore the influence of COVID-19 upsurges, and the presumably associated prothrombotic milieu on STEMI presentations and outcomes in the literature as well as in our single centre experience, aiming to appreciate what would guide future practices.

Methods

This is a retrospective observational analysis performed in Aswan Heart Centre (AHC), Aswan, Egypt. AHC is the only 24/7 primary PCI (pPCI) center in a rural area, serving a population of 1.5 million inhabitants in South Upper Egypt. AHC receives STEMI calls for pPCI, pharmaco-invasive and rescue PCI from a network of 7 pPCI-non-capable facilities within a 130 km radius, with an average of 480 annual STEMI referrals.

In this single-centre study, we evaluated STEMI presentations through the period between May 1st-to-June 30th, 2020 [during the first COVID-19 surge in Egypt]. To contrast them with “non-COVID-surge” controls, we inspected STEMI presentations during the same interval (May 1st-to-June 30th) in 2019, to offset any seasonal or climatic confounders in our specific locality.

After attaining AHC institutional ethical committee, [MS-358-2020], patients’ clinical data including age, gender, conventional risk factors for Coronary Artery Disease (CAD) , data at presentation including initial assessment, baseline laboratory workup, procedural data and outcomes, as well as post-discharge data [30-day clinical outcomes] were reviewed from medical files, tabulated and categorized by date of admission into the control group (May 1st-to-June 30th ,2019) and the COVID-19-surge group (May 1st-to-June 30th ,2020). Any unclear or missing information was completed by contacting the corresponding patient by phone. Data were tabulated anonymously skipping personal identifiers, to waive the need for patients’ consent.

Patients' presentation

Classically in the pre-COVID era, when a patient presents to any of our network centres with established STEMI diagnosis[12], our centre is notified by the patient data (personal data, time of pain onset to diagnosis, clinical profile and risk factors, Killip class, echocardiographic data) with sharing of the ECG over smartphones. According to the clinical status and expected time to transfer, a decision is made for immediate transfer to our centre for pPCI, or (if transfer time is >120 minutes and there are no contraindications to thrombolytics) to administer thrombolysis with either elective transfer for pharmaco-invasive strategy within 24 hours in cases of successful lysis or immediate transfer in cases of failed thrombolytic reperfusion.

During the COVID first peak and enforced by the shortage of personal protective equipment (PPE), our "hub and spoke" system adopted a conservative/modified protocol implying more utilization of pharmacological thrombolysis to minimize patient transfer and preserve PPE. In brief (but more details are in the discussion), onsite thrombolysis was administered for *uncomplicated non-anterior STEMIs* presenting to any pPCI-non-capable centre in our network, with selective subsequent transfer to our centre in cases of failed lysis (<50% resolution of ST and/or persistent chest pain) or post-MI complications (post MI heart failure or post MI angina). All anterior STEMIs were routinely transferred (either immediately for pPCI, or after lysis if the expected transfer time was >120 min). All STEMI patients with hemodynamic instability or thrombolysis contraindication were directly transferred for pPCI.

SARS-CoV-2 testing

By the beginning of COVID-19 pandemic when thresholds for suspicion were still high, our centre did not employ routine polymerase chain reaction (PCR) testing for all STEMI referrals, where testing was selectively ordered based on clinical suspicion.

With subsequent publications about confirmed PCR-positive cases who are asymptomatic (or minimally symptomatic),[13] it is very possible that some undiagnosed SARS-CoV-2 infections existed among our 2020 STEMI cohort. Additionally, there is growing evidence that patients recovered from COVID-19 (and thus become PCR-negative) might have SARS-CoV-2-related late sequalae.[14,15] Hereby, we labelled the May-to-June 2020 STEMIs as the "COVID-era group", presuming that asymptomatic infections and post recovery late sequalae were responsible for many of the observed differences during the COVID-19 upsurge compared to the controls in the pre-COVID-era, despite the low rate of PCR confirmed infections in our cohort.

Statistical analysis

Statistical package for social science (SPSS) software, version 22 for Microsoft Windows (SPSS Inc., Chicago, IL, USA) was used for data analysis. Categorical data were presented as frequency and percentages (n (%)) and correlations among them were analyzed by Chi-square test. Continuous data were subjected to normality testing using Shapiro-wilk test and (if needed) visual assessment of histogram plots; and were presented as mean ± (standard deviation) or median [interquartile range], then were compared using independent samples t-test or Mann-Whitney test as appropriate. A probability p value ≤ 0.05 was considered statistically significant.

Results

In the interval between May 1st, 2020 -to- June 30, 2020, our centre was consulted for 37 STEMI patients from our network centres. Six patients (16%) underwent successful on-site thrombolysis for isolated lateral or inferior uncomplicated STEMI. According to the institutional protocol adopted during the crisis (represented in figure 1 and detailed in discussion), these 6 patients were managed medically in their centres, and because they lead

a complication-free hospitalization (no post-MI angina or heart failure), they were discharged from the admitting facility after a median of 3 days without transfer to our centre. The remaining 31 STEMI patients met at least one of the predefined criteria for transfer. Figure 2 shows a flow chart of STEMI calls and transfers during the first COVID-19 peak.

In contrast to 37 STEMI calls during the COVID-19 surge (COVID-era group), there were 77 STEMI calls and referrals in the corresponding period in 2019, representing the reference workload (Control group). This represents a 52% reduction in STEMI calls to our centre during the COVID-19 first peak in Egypt.

Clinical and demographic data of STEMI patients during the COVID-era were comparable to the control group (represented in table 1). Time delay from the first medical contact (FMC) till reaching the pPCI centre and total ischemic time were significantly longer in the COVID-compared to the control-group, (median [IQR]: 150 [90-360] vs 60 [50-150] minutes; p = 0.001, and 585 [345-1210] vs 412 [270-515] minutes; p = 0.01, respectively). There was no significant difference in patient related time delays (pain onset-to-FMC).

Rates of attempting thrombolysis were comparable in the COVID- and the control-eras (8/37 [22%] vs 14/77 [18%] respectively, p = 0.6). However, failure of thrombolysis was significantly more in the COVID-era (5/8 [63%] vs 3/14 [21%], p = 0.05). STEMI to be secondary to stent thrombosis (confirmed by angiography) was significantly more prevalent in the COVID-era (5 (16%) vs 2 (3%), p = 0.01). Noteworthy that among the 5 cases of definite stent thrombosis (ST) in the COVID-group, 3 had very late (> 1 year) and 2 had late ST (both were >6 months from index PCI). Other data outlining patients' presentation, angiographic features and outcomes are summarized in table 2.

There were 5 (16%) SARS-CoV-2 infections confirmed by PCR testing among the COVID-19 era patients. There were no significant differences between the SARS-CoV-2 positive cases and other patients regarding risk factors, presentation, or outcomes, yet admitting the lack of precision in identifying COVID-19 asymptomatic or recovered cases in our COVID-era group.

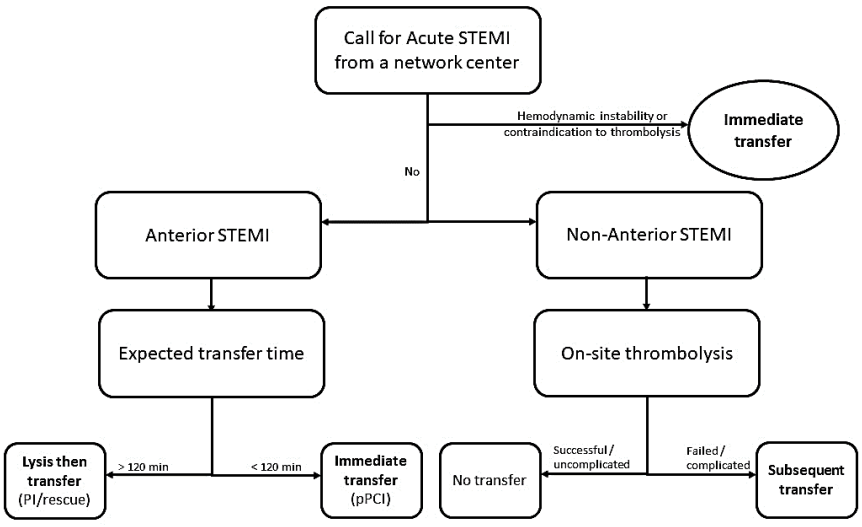

Figure 1: Local institutional policy adopted during the COVID-19 crisis.

PI, pharmaco-invasive strategy; pPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

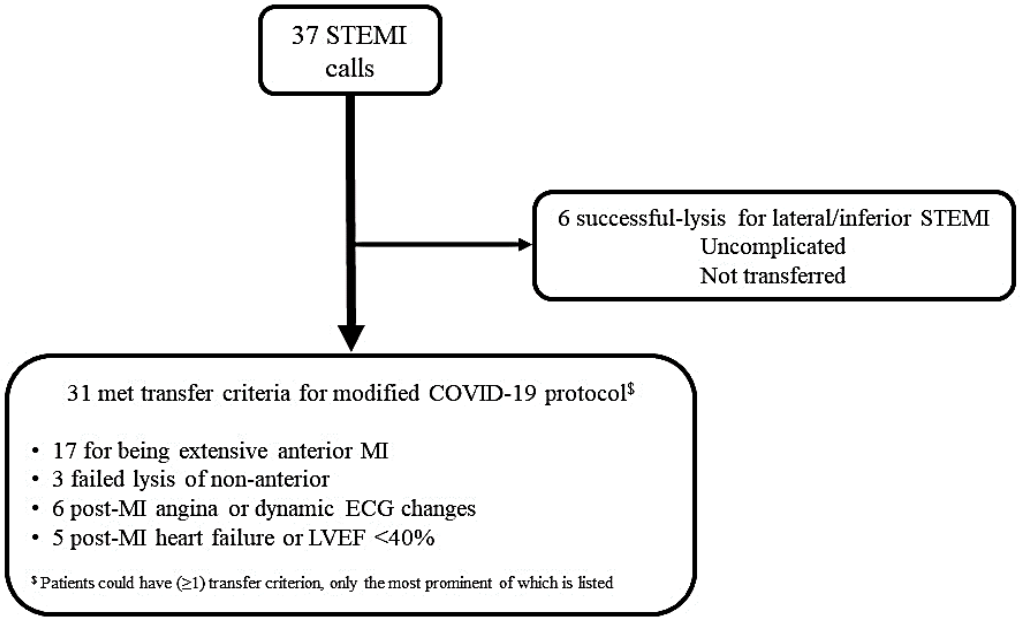

Figure 2: Flow chart for management and transfer during COVID-19 era

STEMI, ST-segment elevation myocardial infarction.

Table 1: Demographic and clinical features of the COVID-19-era and the control group.

	COVID-19 era group	Control-group	*p* value
Age (years)	56 [49-65]	59 [50-69]	0.28
Male gender	25 (81%)	63 (82%)	0.54
Diabetes mellitus	14 (45%)	33 (43%)	0.83
Systemic hypertension	11 (36%)	37 (48%)	0.28
Smoker	20 (65%)	54 (70%)	0.65
Dyslipidemia*	10 (32%)	21 (27%)	0.17
Cumulative RF burden$	3 [2-4]	3 [3-4]	0.36

Data expressed as median [inter-quartile range] or frequency (percentage) as appropriate

Table 2: Clinical data at presentation and angiographic data of the COVID-19-era and the control group.			
	COVID-19 era group	Control-group	*p* value
Pain to FMC (min)	240 [120-600]	240 [120-360]	0.71
FMC-to-pPCI centre (min)	150 [90-360]	60 [50-150]	0.001
Total ischemic time (min)	585 [345-1210]	412 [270-515]	0.01
Peak-Troponin (ng/ml)	4.1 [2.0-8.8]	4.7 [2.2-9.2]	0.74
Peak-CKMB (u/L)	153 [87-323]	211 [102-373]	0.39
Pre-PCI LVEF (%)	40 [35-50]	45 [35-50]	0.43
Anterior MI	21 (68%)	42 (55%)	0.21
Inferior MI	9 (29%)	32 (42%)	0.22
Lateral MI	4 (13%)	4 (5%)	0.16
Isolated posterior MI	2 (7%)	4 (5%)	0.79
Initial thrombolysis strategy	8 (22%)	14 (18%)	0.6
Failed thrombolysis	5 (63%)	3 (21%)	0.05
Large thrombus burden	16 (52%)	29 (38%)	0.19
Culprit = ST	5 (16%)	2 (3%)	0.01
COVID-19 positive	5 (16%)	0	
Data expressed as median [inter-quartile range] or frequency (percentage) as appropriate.			

Discussion

In the present study, we document the complex influence of COVID-19 upsurge on STEMI referrals in a pPCI referral centre in Egypt. Compared to the controls in the same period of the previous year, STEMI referrals during the COVID-19 first peak showed significantly higher rate of thrombolysis failure and of STEMIs secondary to stent thrombosis (ST), that might point to a hypercoagulable status related to the COVID-19 era. Witnessing recurrent and more aggressive SARS-CoV-2 peaking waves dominated by the emerging new variants, we opted to further analyze these observations to guide practice in face of recurrent crises.

New SARS-CoV-2 variants that are more serious, more infective and potentially less responsive to contemporary vaccines,[16–18] have dominated many regions in the world causing overwhelming subsequent waves of SARS-CoV-2 infections exceeding what was seen during the first wave.[19,20] These upsurges in the rates of spread consumed all the reserves for many health systems and represented national crisis, similar -or even worse than- what was met during the commence of the pandemic. For the fears that such devastating burden may enforce compromises and/or declines in essential medical services like primary PCI similar to the beginning of the pandemic, we liked to demonstrate the observations we had in our centre during the first peak.

When COVID-19 started to peak in Egypt, our hub-and-spoke system

developed a "modified STEMI reperfusion protocol" adaptive with the challenging situation, as many other national and international centres.[21–23] This adaptive protocol (Figure 1), employed onsite thrombolysis for uncomplicated non-anterior STEMIs presenting to any pPCI-non-capable centre in our network. Selective subsequent transfers for pPCI to our centre took place in cases of failed lysis or post-MI complications. However, anterior STEMIs were routinely transferred (either immediately for pPCI, or after lysis if expected transfer time was >120 min). All STEMI patients with hemodynamic instability or lysis contraindication were directly transferred for pPCI.

Despite the temporal variation for COVID-19 first surge in different regions across the globe (that was in January-February 2020 in China, March-April 2020 in Europe and USA, while May-June 2020 in Egypt), re-emergence of thrombolysis as an alternative reperfusion option was deemed necessary in many parts of the World.[3,6,22,24] Onsite thrombolysis for STEMIs presenting to pPCI-non-capable centres (as an alternative to immediate transfer), arguably had the advantage of minimizing patients transfer between hospitals, reducing consumption of PPE, reducing exhaustion of medical resources, and limiting exposure of healthcare personnel.

Nevertheless, in our practice, rates of failure of thrombolysis during the first COVID-19 peak were 3 folds as in the corresponding control group despite the comparable clinical profiles and patient-related delays (63% vs 21%, p = 0.05). This goes in line with the numerical higher rate of encountering large thrombus burden (according to TIMI classification[25]) in the COVID- compared to the control-group. Similar data of thrombolysis failure, paralleled with longer hospital stay, increased patients' morbidity and total mortality were reported from real practice and predictive models published amid the COVID-19 crisis.[26,27] These impactful findings raised a lot of concerns against expanding the utilization of thrombolysis as an alternative to pPCI.[24,28]

Additionally, there are many occasions during COVID-19 surges where thrombolysis would cause more harm than benefit. STEMI mimicking diagnoses were increasingly reported in the COVID-19 experiences.[29,30] The rate of STEMI diagnoses found to have non-obstructive coronary arteries in subsequent angiograms (thus excluding type 1 MI) reached 39.3% in a case series published from Northern-Italy during the first COVID-19 peak.[7] In addition, presentations of type 2 MI, that is possibly precipitated by the hypoxemia, fever, intense systemic inflammation and tachycardia were frequently encountered among COVID-19 critically ill patients.[4,29] In such cases, thrombolysis would lead to pure harm devoid from any potential benefits, compared to the standard angiography-guided management.

Moreover, considering the high rate of thrombolysis failure mandating subsequent transfer for rescue PCI, thrombolysis-based strategies compared to the default immediate transfer for pPCI, lead to

prolonging ischemic time, worsening patients' outcomes, increasing patients' morbidity and mortality and hospital stays and costs, while failing the expectations to preserve PPE and minimize medical team exposure. Accordingly, consensus statements released from the Society for Cardiovascular Angiography and Interventions (SCAI) and the American College of Cardiology (ACC) ensured that priority of pPCI over thrombolysis should not be interchanged during the COVID-19 pandemic.[30,31]

Higher rates of stent thrombosis

In our COVID-era STEMI group, we encountered a higher-than-usual rate of type 4b MI, (proved by angiography to be due to stent thrombosis (ST)) compared to their corresponding control (16% vs 3%, p = 0.001). All our five ST cases were >6 months post PCI (3 had very late ST, and 2 had late ST), and none of them prematurely discontinued the P_2Y_{12} inhibitor therapy. Higher rates of ST were increasingly reported during the COVID-19 waves, despite not all of these cases had confirmed SARS-CoV-2 infections.[10,32] A report published amid the COVID-19 crisis stated that rates of ST reached up to 13% of the PCI workload, compared to a traditional annual rate of late and very late ST ranging between 0.2-to-2%.[10]

SARS-CoV-2-related thrombogenicity

Higher rates of thrombolysis failure, stent thrombosis and large thrombus burden were repeatedly reported during COVID-19 surges, and were significantly exceeding the numbers of SARS-CoV-2 positive cases in the corresponding cohorts.[6,10,26,27] It should be suspected that such consistent increase compared to conventional rates, is correlated to a hypercoagulable status common with -and perhaps persisting for some time after- SARS-CoV-2 infections. The high rate of asymptomatic SARS-CoV-2 infections and the growing evidence on late sequalae in recovered cases (i.e. after becoming PCR negative), can explain the discrepancy between the prevalent hypercoagulable manifestations "presumably related to COVID-19", as opposed to the fewer numbers of PCR-confirmed SARS-CoV-2 infections.[13,33]

SARS-CoV-2 infection has been affirmed as a systemic condition involving multiple organs rather than a simple respiratory viral illness.[34–36] Enhanced thrombogenicity is believed to play an important role in the pathogenesis of COVID-19 systemic inflammation and complications. Frequently, microthrombi were found disseminated in multiple organs (including heart, liver, kidney besides the lungs) in autopsies of COVID-19 mortalities suggesting a mechanistic role in disease fatality.[37,38]

The full pathogenesis of COVID-19-related enhanced thrombogenicity is not very clear, yet there are plenty of potentially involved pathways that are supported by clinical and/or lab findings. Direct viral invasion of the endothelial cells through the angiotensin converting enzyme (ACE) receptors resulted in

profound endothelial dysfunction, promoted cell damage, inflammation and thrombosis.[39,40] In another report, SARS-CoV-2 RNA was detected in platelets of advanced COVID-19 cases, with proven hyperactive aggregation and adhesion functions of the infected platelets.[41] Additionally, the manifest systemic inflammation seen in COVID-19 cases, with a perceived procoagulant role of the cytokine storm has an overwhelming evidence to support. .[42–44] The SARS-CoV-2 -associated overstimulation of Interleukin-6, other inflammatory mediators and cytokines, was proportionally correlated to higher levels of fibrinogen in critically-ill COVID-19 cases.[42] Moreover, these patients were consistently found to have abnormally high levels of other procoagulant factors (D-Dimer and factor VIII), paralleled with downregulation of natural anti-coagulants (including: protein C, protein S and antithrombin).[42–44] Lastly, the direct effect of inflammatory cytokines on atherosclerotic plaques can mediate local plaque destabilization and rupture with subsequent acute thrombotic occlusion. This theory is highly incriminated in SARS-CoV-2 linkage to promoting acute peripheral arterial ischemia, cerebrovascular accidents and myocardial infarctions.[40,45] Thus, SARS-CoV-2-related procoagulant influence is ascertained, and it can explain the enhanced thrombogenicity, and subsequently, the reduced likelihood of successful lysis seen during COVID-19 surges.

Implications of the contemporary challenges

Admitting the contemporary threats of new or recurring crises by the emerging new variants, it might be wise for cardiologists to exert every effort to keep pPCI the default reperfusion strategy for STEMI (if it can be offered in a timely fashion), as the expected benefits from prioritizing “on-site thrombolysis” are plagued by high failure rate coupled with a non-justifiable excess bleeding risk for the patients. Further studies are needed to evaluate if it might be wise to be more in favor of prolonging dual antiplatelet therapy in patients with previous PCI and high ischemic risk amid COVID-19 surges.

Limitations

This is a single centre study with a relatively small number of patients, which represents one of the limitations in our study. The retrospective nature of the analysis represents another limitation. We admit the imprecise identification of the number of PCR-confirmed SARS-CoV-2 infections, due to unemployment of routine PCR testing to all STEMI patients in our centre by the earlier times of the pandemic. However, the common hypercoagulable manifestations during SARS-CoV-2 surges were consistently more prevalent than numbers of confirmed cases, possibly explained by undiagnosed asymptomatic cases and/or because of late sequalae in recovered cases. Comparing rates of angiography-confirmed stent thrombosis involved all the STEMI patients during pre-COVID era versus only the referred

STEMI cases during the COVID-era (excluding the 6 medically managed cases). This is another limitation in our study; however, we assume it would not defy the derived conclusion.

Conclusions

COVID-19 infections have been tied to systemic inflammation with a secondary prothrombotic status. During COVID-19 surges, prothrombotic manifestations are disproportionately more prevalent than numbers of confirmed infections, possibly because of the high rates of undiagnosed asymptomatic cases or as late sequalae in recovered cases. The enhanced thrombogenicity witnessed amid COVID-19 surges, perhaps promotes late and very late stent thrombosis and reduced success of thrombolytic reperfusion. Anticipating recurrent overwhelming waves with the emergence of SARS-CoV-2 new variants, it is very prudent to explore learning points from the prior COVID-19 experiences to improve our management strategies.

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