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How did the COVID-19 pandemic affect the referral patterns for SPECT myocardial perfusion? A single center experience

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ABSTRACT

Objective(s): We evaluated the impact of the COVID-19 pandemic on the number of referrals for SPECT myocardial perfusion imaging (SPECT-MPI) as well as changes in the clinical and imaging characteristics.

Methods: We respectively reviewed 1042 SPECT-MPI cases performed in a 4-month period during the COVID-19 pandemic (PAN; n=423) and compared their findings with those acquired in the same months before the pandemic (PRE; n=619).

Results: The number of stress SPECT-MPI studies performed during the PAN period significantly dropped compared to the number of studies carried out in the PRE period (p = 0.014). In the PRE period, the rates of patients presenting with non-anginal, atypical and typical chest pain were 31%, 25% and 19%, respectively. The figures significantly changed in the PAN period to 19%, 42%, and 11%, respectively (all p-values <0.001). Regarding the pretest probability of coronary artery disease (CAD), a significant decrease and increase were noticed in patients with high and intermediate pretest probability, respectively (PRE: 18% and 55%, PAN: 6% and 65%, p <0.001 and 0.008, respectively). Neither the rates of myocardial ischemia nor infarction differed significantly in the PRE vs. PAN study periods .

Conclusion: The number of referrals dropped significantly in the PAN era. While the proportion of patients with intermediate risk for CAD being referred for SPECT-MPI increased, those with high pretest probability were less frequently referred. Image parameters were mostly comparable between the study groups in the PRE and PAN periods.

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Introduction

The Wuhan-originated RNA-virus, coronavirus (nCoV), was termed "SARS-CoV-2" by WHO as the agent accounting for COVID-19 pandemic in December 2019 (1). The first known case of COVID-19 in Iran was reported in 19th Feb 2020 in Qom, heralding Iran as one of the first countries facing the pandemic (2). The pandemic had a significant global burden on healthcare systems demanding immediate re-definition of departmental organization, imaging programs, guidance and best practices for re-establishment of emergent and non- emergent care in all fields, of which nuclear cardiology studies are no exception(3-5).

The incubation period for COVID-19 is usually about five days (6). Given the multi-systemic nature of the disease, cardiac involvement is common, affecting up to one-fifth of the cases (7). The cardiac manifestations of COVID-19 are acute coronary syndrome, heart failure, cardiogenic shock, arrhythmias, and myocarditis, to name a few, with mortality rates of the latter reaching 7% (8-12).

There is a wide geographic variation in the rates and triage of patients with coronary artery

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disease (CAD) (13-16). Moreover, various national protocols for non-invasive imaging in the COVID-19 era (17, 18) and the difference in the burden of COVID-19 infection also causing cardiac symptoms, may impact the number of patients referred for SPECT myocardial perfusion imaging (SPECT-MPI). While a recent systematic review identified a collateral cardiovascular damage of the pandemic, especially in low-middle income countries, no data from Iran was presented (19). Therefore, we assessed the impact of COVID-19 pandemic on the number of referrals for SPECT-MPI as well as changes in the clinical and imaging characteristics.

Methods

Patient population

We retrospectively reviewed all patients who were referred to our center for SPECT-MPI in the COVID-19 pandemic (PAN; N=423), between June and September 2020, and in the same months prior to the pandemic in 2019 (PRE; N=619). General clinical data regarding the patients' age, sex, type of chest pain, pretest probability of CAD, and cardiovascular risk factors (hyperlipidemia, hypertension, diabetes mellitus, and smoking) were recorded. Also, the results of previous exercise tolerance test (ETT), left ventricular ejection fraction (LVEF) as determined by echocardiography, and data regarding prior history of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) were documented.

Clinical definitions

Classification of chest pain was carried out based on ACC/AHA 2013 on multimodality appropriate use criteria (20). Pre-test probability of CAD was categorized according to Diamond and Forrester pretest probability of CAD using age, sex and type of chest pain (20).

Hyperlipidemia, hypertension, (21) conditions, total cholesterol ≥240 mg/dL, blood pressure ≥140/90 mmHg, and FBS ≥126 mg/dL) (21) Current or prior smoking and/or tobacco use was regarded as positive smoking history. Positive family history was defined according to AHA/ACCF 2011 practice guidelines for secondary prevention of patients with CAD (22).

Scan protocol

SPECT-MPI was performed according to the EANM and ASNC guidelines (23, 24). Briefly, in one-day protocol, the rest phase imaging was performed 30-90 min following administration of 370 MBq of ^{99m}Tc-MIBI. Later, the stress phase was done 15-30 min after the injection of 1110 MBq of ^{99m}Tc-MIBI. For the 2-day protocol, both phases were performed when 740-1100 MBq of ^{99m}Tc-MIBI was injected. During the COVID-19 pandemic, only vasodilator stress tests were performed in accordance with the local practice guidelines. The protocol was also later supported by the international guidelines and a systematic review in this field (17).

Image acquisition

Gated SPECT-MPI was performed using a dual head variable angle gamma camera (GE Discovery NM 630) with low-energy high-resolution collimator. The patients were in supine position for both phases of the study. Recordings were obtained in 32 projections (20 sec. per projection, matrix=64×64, magnification=1.45).

The photopeak was centered for 140 keV and a 15% energy window level. For gating, 8 frames per cardiac cycle with a 20% acceptance window were applied. The images were reconstructed using filtered back projection and Butterworth filter (order=5, cut-off frequency=0.55).

Image interpretation

The imaging/interpretation parameters for each patient, namely, summed stress score (SSS), summed rest score (SRS), summed difference score (SDS), calculated LVEF, post-stress LV drop, presence of dilated LV cavity, and transient ischemic dilatation (TID) were reviewed by two board-certified nuclear medicine specialists, using the 17-segment method (25). Furthermore, the type of stress imaging protocol (i.e. exercise or pharmacological test), ECG changes during the stress, and presence of perfusion defects (either ischemia or infarction) were also documented. For the last two aforementioned parameters, the total perfusion deficit (TPD) provided automatically by the QGS software was used as an ancillary item and the visual interpretation was the cornerstone for labeling the type of the perfusion abnormalities. Abnormal thresholds for calculated LVEF were set as <52% in men and <62% in women, according to our previous experience (26). Significant reversible TPD was defined as SDS ≥7, roughly equivalent to ischemic TPD ≥10% of the LV mass (27).

Statistical analysis

SPSS statistics package (IBM corp., Armonk, NY, USA; ver. 19) was used for statistical analysis. Continuous variables were expressed as mean±SD or median (range) based on presence or absence of normal distribution for a given variable. Categorical variables were mentioned by percentage and frequency. The PRE and PAN study time periods were compared using student T-test or Mann-

Whitney U test and Chi-square or Fisher exact tests for continuous and categorical groups, respectively. Two-tailed p-values<0.05 were considered significant.

Results

The mean age of the patients in PRE and PAN time slots were 57±11 and 55±12 years, respectively (p=0.059). The patient population was mainly female in both time periods (PRE: 69%, PAN: 70%). A significant drop in the number of referrals was noted in the PAN period (PRE: 619, PAN: 423, p=0.014). No difference was observed between the two time periods in terms of cardiovascular risk factors, except for smoking which increased significantly during the COVID-19 pandemic (PRE:13%, PAN:18%, p=0.014). The number of patients with non-anginal (PRE: 31%, PAN: 19%, p<0.001) or typical (PRE: 19%, PAN: 11%, p<0.001) chest pain decreased significantly during the COVID-19 pandemic, while atypical chest pain cases increased significantly (PRE: 25%, PAN: 42%, p<0.001). Regarding the pretest probability of CAD, during the COVID-19 period, cases with high pretest probability decreased (PRE: 18%, PAN: 6%, p<0.001) while those with intermediate risk increased significantly (PRE: 55%, PAN: 65%, p=0.008). The changes in the remaining risk categories were modest (Table 1).

Table 1. Demographic features and risk factors of the patients in the COVID-19 (n = 423) and non-COVID (n = 619) time periods

	Non-COVID-19 period	COVID-19 period	p-value
Age (years)	57 ± 11	55 ± 12	0.059
Gender			
Male, n (%)	193 (31)	128 (30)	0.785
Female, n (%)	426 (69)	295 (70)	
Type of chest pain			
Non-anginal, n (%)	189 (30.5)	79 (18.6)	<0.001
Atypical, n (%)	152 (24.5)	176 (41.6)	<0.001
Typical, n (%)	119 (19.2)	46 (10.8)	<0.001
No chest pain, n (%)	159 (25.6)	122 (28.8)	0.286
Pretest probability of CAD			
High risk, n (%)	82 (17.8) **a**	18 (6) a	<0.001
Intermediate risk, n (%)	252 (54.8) **a**	194 (64.5) a	0.008
Very low/Low risk, n (%)	126 (27.4) **a**	89 (29.5) a	0.564
CAD risk factors			
Hyperlipidemia, n (%)	264 (42.6)	167 (39.4)	0.305
Hypertension, n (%)	360 (58.4) **b**	225 (53.1)	0.098
Diabetes mellitus, n (%)	184 (29.8) **b**	134 (31.6)	0.538
Smoking, n (%)	79 (12.8) **b**	78 (18.4)	0.014
Previous diagnostic tests			
Previous ETT, n (%)	173 (27.9)	130 (30.7)	0.332
Positive, n (%)	57 (33)	52 (40)	0.227
Echo-EF, mean ± SD	55 ± 8	54 ± 9	0.199
Previous CAD history			
PCI, n (%)	53 (8.5)	39 (9.2)	0.739
CABG, n (%)	51 (8.2)	34 (8)	>0.999

a After excluding patients with no chest pain (mainly referred due to exertional dyspnea), the denominator for non-COVID-19 and COVID-19 timeslots was changed to 460 and 301, respectively.
b Denominator is 616.
CABG = Coronary Artery Bypass Grafting, ETT = Exercise Tolerance Test, PCI = Percutaneous Coronary Intervention

The type of SPECT-MPI protocol as well as scintigraphic findings are summarized in Table 2. During the pandemic, one score increase in the median of SDS was observed (p=0.035).

However, the rate of patients with either ischemia or TPD ≥10% was comparable in the two time periods. A slight reduction, i.e. ~3%, in the median calculated LVEF was noticed in the PAN study period (p=0.001) while the rate of abnormal LVEF and the EF values determined by echocardiography were similar. No statistically significant difference was observed on the rate of myocardial infarction or cardiomyopathy between the two study periods. The rates of ischemia, number of affected territories, severity of ischemia, and TID were comparable in both PRE and PAN time periods. Moreover, the rate of LV cavity dilation, and gating abnormalities were similar between the two time periods. There was a significant decline in the rate of stress-induced ECG changes in the PAN period (PRE: 3.7%, PAN: 0.9%, p=0.005).

Subgroup analysis revealed that this finding was mainly attributed to the omission of exercise stress test in the PAN time slot (PRE: 2.1% vs. PAN: 1%, p=0.197; the subgroup analyses are available in supplemental tables 1 and 2). No significant difference was noticed in the rate of stress-only (i.e. single phase) imaging between the two time slots (PRE: 10.9%, PAN: 13.1%, p=0.281). Four patients (0.9%) had a

history of PCR-confirmed severe COVID-19 infection requiring hospitalization, one of which exhibited myocardial ischemia (SDS=6).

Table 2. Type of SPECT-MPI and its findings in the COVID-19 (n = 423) and non-COVID (n = 619) time periods

	Non-COVID-19 period	COVID-19 period	p-value
SPECT-MPI study protocol			
Exercise, n (%)	82 (13.2)	0	<0.001
Dipyridamole, n (%)	530 (85.6)	418 (98.8)	<0.001
Dobutamine, n (%)	4 (0.6)	0	<0.001
Rest TNG, n (%)	3 (0.5)	5 (1.2)	<0.001
Type of the radiotracer			
^{99m}Tc-MIBI, n (%)	619 (100)	408 (96.5)	
Thallium-201, n (%)	0	15 (3.5)	
Gated SPECT-MPI findings			
Ischemia, n (%)	148 (24)	93 (22)	0.501
Significant ischemia, n (%) **a**	32 (5.2)	30 (7.2)	0.229
Infarction, n (%)	44 (7)	34 (8)	0.632
SSS (Median, Range)	2, 0-38	2, 0-50	0.174
SRS (Median, Range)	1, 0-38	1, 0-44	0.067
SDS (Median, Range)	0, 0-24	1, 0-34	0.035 **b**
MPI-EF (Median, Range)	70 (13-100)	67 (15-97)	0.001
LV cavity dilation	14 (2.3)	16 (3.7)	0.186
Abnormal LVEF, n (%) **c**	120 (19.3)	94 (22.2)	0.275
TID, n (%)	3 (0.5)	6 (1.6)	0.167
Post-stress LV drop ≥5%, n (%)	13 (2.4)	10 (2.8)	0.830
Gating abnormality, n (%)	67 (10.8) **d**	58 (13.7)	0.372
ECG changes, n (%)	23 (3.7) **d**	4 (0.9)	0.005

a Defined as SDS ≥7
b Mean ranks for PRE and PAN timeslots were 442.7 and 477.4, respectively .
c <62% for women and <52% for men [Dabbagh]
d Denominator for ECG changes and gating abnormality was 615 and 616, respectively. Denominator for TID and stunning was 548 for PRE and 363 for PAN, after excluding patients undergoing stress-only study .
LVEF = Left Ventricular Ejection Fraction, SSS = Summed Stress Score, SRS = Summed Rest Score, SDS = Summed Difference Score, TID = Transient Ischemic Dilation, TNG = Sublingual Nitroglycerine

Discussion

In line with previous reports, the number of SPECT-MPI studies that were carried out at our department was dramatically reduced by more than 30% during the COVID-19 pandemic as compared to the corresponding months prior to the pandemic (28, 29). Less referral for SPECT-MPI is most likely due to change in the practice patterns during the pandemic. For example, high-risk patients might have undergone invasive procedures and the referral of low-risk patients for SPECT-MPI might have been deferred considering the logistics and circumstances in the COVID-19 era. This notion is supported in our study by a decline in the rate of patients being referred for SPECT-MPI with either typical or non-anginal chest pain. The reduction in the referral rate of patients with high-risk CAD is also compatible with this finding. Moreover, ischemic patterns were less frequently observed in the high-risk population during the pandemic time slot as compared to that of during the PRE time period (51.2% vs. 33.3%, p<0.001). This finding reaffirms that those in the high-risk category, even if referred, were marginally intermediate-high risk for CAD.

Given the distressful situation of the COVID-19 pandemic, it is not surprising to observe changes in the rate of smoking during the pandemic. Although this finding may also be a mirror of changes in the referral patterns, several studies have supported a surge in the rate of cigarette smoking during the lockdown (30-32). Yet, a systematic review in this field mentioned a heterogeneity among studies alluding to mixed results in the smoking behavior during the pandemic (33, 34). We also found an increasing trend in the rate of hypertension in the COVID-19 era which is also in line with a surge of metabolic diseases in other studies. Again, these findings are likely due to lifestyle changes (e.g. less physical activity) along with low-level chronic stress in the COVID-19 era (35).

The rate of abnormal MPI, demographic characteristics, and clinical risk factors, with the exception of smoking, were not significantly different from the pre-pandemic time slot. Since the majority of the patients being referred for SPECT-MPI have an intermediate risk of CAD, it is reasonable to see no change in the rate of the above mentioned variables in the intermediate-rich population of the pandemic (28, 29). The percentage of abnormal MPI reading in our study was 26% with no statistically significant difference among the two periods and roughly equals to the results by Nappi et. al (PRE:34% vs. PAN:36%) and Hasnie et. al (PRE:27% vs. PAN:31%) in both periods (28,29).

It should be emphasized that we only employed dipyridamole stress MPI during the COVID-19 period. This measure, as described previously, was to avoid the risk of droplet exposure led by exercise stress imaging (4). Given the heterogeneity of stress tests in the PRE period, one may speculate whether our results would be replicated if we have compared only the study findings of the dipyridamole subgroup in the PRE time slot with that of PAN period. Our re-analysis considering this approach yielded the same results, with the exception of age (Supplemental Tables 1 and 2). Younger patients tended to be more referred in the PAN period. Whether subclinical/mildly symptomatic COVID-19 infection with atypical cardiac symptoms contributed to this finding is unknown to us.

We also observed slight reduction in the calculated LVEF and mild increase in the SDS during the pandemic time slot. However, other imaging parameters pointing to either ischemia or infarction were not concordant with these findings. While these may point to some subtle changes owing to lockdown, chances are high if these findings are merely artifactual.

This study was neither designed nor powered to assess the SPECT-MPI changes in patients with COVID-19. Yet, ~1% of our patients were affected by severe COVID-19, reflecting the magnitude of the pandemic even showing its presence in daily routine nuclear medicine studies.

Our study suffers from a number of limitations; apart from its retrospective nature and relatively limited sample size, no access to the follow up data, no available information regarding the indications for referral, lack of data regarding body mass index, and detailed ECG changes during stress SPECT-MPI is the main shortcomings of the current study.

Conclusion

In conclusion, the number of referrals dropped significantly in the PAN era. While the proportion of patients with intermediate risk for CAD being referred for SPECT-MPI increased, those with high pretest probability were less frequently referred. Image parameters were mostly comparable between the study groups in the PRE and PAN periods.

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