Cardiac Electrical Vulnerability after Acute Myocardial Infarction Associated with Respiratory Infections

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Heart rate variability and the presence of late potentials are independent predictor factors for cardiac death and electrical vulnerability of the ischemic myocardium, especially after myocardial infarction(MI). Respiratory infection are known to be associated with MI both through direct action of the pathogen and by altering the hemodynamic status, through tachycardia and a rise in myocardial oxigen demand. Our paper wants to highlight that respiratory infection during subacute and late recovery phase of myocardial infarction can aggravate the electrical vulnerability of the myocardium and increases the arrhythmic risk. We analysed heart rate variability and the presence of late potentials on signal-averaged ECG in patients who developed acute respiratory infection after MI. All parameters of heart rate variability were signifficantly decreased in our target group. Incidence of late potentials did not differ between the two groups, meaning that the electrophysiological substrate of arrhythmias was not influenced by respiratory infection. Ventricular arrhythmias were more severe and frequent in the infection group. Respiratory infectious disease in early and late recovery phase after acute myocardial infarction, increases the risk of life threatening arrhythmias. It must be emphasized the need to consider prevention and early treatment of respiratory viral or bacterial infections, particularly in patients with cardiac ischemic disease .

Keywords: respiratory infections, electrical vulnerability, late potentials, RR variability

There is a strong, biunivocal link between respiratory infections and major cardiovascular events[1,2]. The benefits of lowering the incidence of upper respiratory tract infections (URTI) , both by treating and preventing them, can be substantial[3,4].

URTI can worsen the oxygen imbalance in the ischemic heart by increasing oxygen demand, with more pronunced ischaemia, resulting in development and maintenance of ventricular ectopic beats(VEB). Respiratory infections through the direct action of the pathogen are involved in the ischemic mechanism of the arrhythmogenic substrate, inducing life threatening ventricular arrhythmias[5]. At the same time, low grade fever, hypoxia and persistent tachycardia alters the heart rate variability(HRV), ventricular filling and coronary perfusion. An increase in heart rate may unmask late potentials in patients prone to malignant ventricular arrhythmias [6]. The HRV and the presence of late potentials(LP) are independent predictors of cardiac ischemic death by arrhythmic events. The alteration of the arrhythmic parameters seen in MI patients with respiratory infections, places the last one betwen the aggravating and precipiting factor involved in cardiac morbi-mortality[7].

Experimental part

Materials and method

We selected for our retrospective study, during a three years period, betwen January 2011 to January 2014 patients that were diagnosed with acute myocardial infarction (AMI) and had developed an URTI during admission. They were followed for a period of 3 months. The study group (URTI) consisted of 54 patients, and a control group consisting of 52 patients (non-URTI) with similar characteristics, but no URTI. All 106 patients included in the study were diagnosed with AMI according to the 4th universal definition of myocardial infarction: symptoms typical of myocardial infarction, new electrocardiographic changes (persistent ST segment elevation), parietal wall motion abnormalities consistent wit AMI, an elevated troponin above the 99th percentile with dynamic changes. Patients with anterior AMI (Topol 3) and inferior AMI(Topol 4,5) were chosen due to their relative frequency and theoretical equal mortality at 1 month. Patients received pharmacoinvasive therapy, followed by anticoagulant, double antiplatelet therapy, high dose statin, betablocker, angiotensin converting enzyme inhibitors and also metabolic modulator, with prowen cardioprotective effects against myocardial ischemia[8], all of this as standard guidelines based therapy. All patients benefited from electrocardiography(12 leads ECG) and signal averaged-ECG wich determined RR variability and late ventricular potentials. Also, transthoracic echo-cardiography (TTE), ECG Holter monitoring and serial blood samples were analysed. Baseline renal function was assessed using the CKD-EPI creatinine equation[9]. The panel of biomarkers availabled for monitoring and for the prognosis of acute kidney injury(AKI) were limited at that time and nowadays numerous studies have proven the importance of microRNAs in this field[10,11]. Dyslipidemia, determined through serum levels, (including high levels of

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total cholesterol, triglycerides, LDLc and low levels of HDLc) is one of the factors responsible for the increased cardiovascular risk associated with CKD and also with progression of kidney injury[12].

URTI was diagnosed from a clinical point of view based on specific symptoms of an upper airway infection: cough, sore throat, nasal congestion, low grade fever, headache, sneezing, including laryngitis and tracheitis at 3 days or more from the admission[11].

AMI-acute myocardial infarction; CKD, chronc kidney disease; eGFR-estimated glomerular filtration rate; ESR-erythrocyte sedimentation rate; CRP- C reactive protein; LVEDD/LVESD – left ventricular end diastolic/systolic diameter; LVEDV/LVESV – left ventricular end diastolic/ systolic volume .

Between the two groups there were no significant statistical differences regarding sex, AMI teritory, echocardiographic parameters, BMI, and the presence of other risk factors(HTN, DM, dyslipidemia) as seen in table 1. A higher age, CKD and a smoking status were more significantly present in the URTI group and they also had very significantly higher heart failure symptoms manifestations and elevated inflammation markers (table 1) .

HRV represents an expression of the balance between sympathetic and parasympathetic activities. Impaired RR variability means a reduction in parasympathetic control, but it can also signify an imbalance in the autonomous nervous system. Nervous system imbalance is strongly correlated with electrical instability of the myocardium, patients having an increased risc of sudden cardiac death. The physiopathological explanation of this relationship is still a debate among researchers, but is unanimously accepted that a reduction in vagal tonus increases the arrhythmogenic substrate via sympathetic activity. For this reason HRV and its components represent a predictor in sudden cardiac death.

The equilibrium between sympathetic and parasympathetic arms of the vegetative nervous system is illustrated by HRV components. In high frequency range, RR variability is modulated by parasympathetic nervous system and it corresponds to parasympathetic tonus, but in low frequency range, RR variability is both under parasympathetic and sympathetic influences. HRV was performed with a 12 channel Hellige electrocardiograph which allows for RR variability quantification, both in time domain and frequency domain.

Parameters were calculated using *LR* software, that recognises and eliminates atypical QRS variability, including those attributed to supraventricular premature beat through analysis algorithms. Although the software is capable of eliminating most of these artefacts, for accurate data aquisition, qualified human supervision was also performed. In addition, this software allows, through rapid Fourrier analysis, the recording of the entire spectrum of frequency and evaluates the separation between spikes of high frequency(HF 0.15-0.5Hz) and low frequency(LF 0.01-0.15HZ). This spectrum of frequency variation is performed during a 2 minute analysis window. For easy interpretation we have utilised for time domain a standard deviation(TSD) parameter with normal range of 50 ms or greater.

Recording the late ventricular potentials was performed with the same device, with 35Hz filter, recording for 2 minutes (noise levels at <0.5uV). It was taken into consideration if one of the following was present: positive filtered QRS with QRSd>120 ms, RMS40(Root-Mean-Square Voltage of terminal 40 ms) < 20 uV or LAS(Low amplitude signal duration) > 40 ms.

Late potentials are defined as waves with low amplitudes and high frequency that appear in the terminal part of the QRS complex, widening its base and extended into the ST segment. The alteration of electric properties during ischemia is realised through delayed depolarization,

Parameter	URTI group n=54	Non-URTI group n=52	p
Male gender	38(70.37%)	35(67.30)	0.834
Mean age (years)	67.21±6.92	64.62±9.81	0.045
AMI (teritory):			
Anterior AMI (Topol 3)	35(64,81%)	29(55.76%)	0.427
Inferior AMI (Topol 4,5)	19(35,19%	23(44.24%)	0.427
History of :			
Arterial hypertension (HTN)	36(66.66%)	39(75%)	0.396
Diabetes mellitus (DM)	29(53.70%)	21(40.38%)	0.180
CKD (eGFR <90ml/min/m²)	21(38.88%)	10(19.23%)	0.033
Cigarette smoking	34(62.96%)	20(38.46%)	0.019
Dyslipidemia	38(70.37%)	35(67.30%)	0.834
Transthoracic echocardiography:			
Ejection fraction (Simpson EF%)	42.5 ±3.79	43.6±4.75	0.173
LVEDD (cm)	5.71±0.47 4.62±0.32	5.64±0.41	0.632
LVESD (cm)	89.04±14.57	4.47±0.28	0.578
LVEDV (ml)	52.64±7.79	86.63±13.75	0.484
LVESV (ml)		48.34±8.01	0.286
Clinical and Laboratory data :			
BMI (kg/m²)	27.16 ± 4.12	26.16 ± 3.82	0.138
Heart failure symptoms	41(75.92%)	11(21.15%)	<0.001
ESR (mm/1h)	43.21±12.45	27.56±11.21	0.004
Fibrinogen (mg%)	670.45±35.67	455.23±45.78	0.046
CRP (mg%)	6.98±0.46	4.09±0.25	0.003

Table 1
STUDIED GROUPS BASELINE CHARACTERISTICS

AMI-acute myocardial infarction; CKD, chronc kidney disease; eGFR-estimated glomerular filtration rate; ESR- erythrocyte sedimentation rate; CRP- C reactive protein; LVEDD/LVESD – left ventricular end diastolic/systolic diameter; LVEDV/LVESV – left ventricular end diastolic/systolic volume.

slowing of conduction impulse, inflammatory oedema from necrotic tissue and fibrous scar, all of wich create areas with slow conduction, creating a re-entry circuit. Late potentials represent the surface expression of nonhomogenous myocardial tissue which alters conduction and alter the depolarisation. This speckled tissue represent the morphological basis of re-entry and the risk of developing malignant arrhythmias. The VLPs were found highly predictive of cardiac events, in particular, arrhythmic events, in patients with acute myocardial infarction[13].

A 24h Holter monitoring was performed in the 3th to 6th day from the AMI, concomitant with the URTI episode. The device was a 5 channel Labtech CardioSpy, with DII, V5-V6 leads, and the results were classified according to Lown classes.

Statistical analysis

GraphPad Software, Inc 3.1 was used for the statistical analysis. To assess the statistical significance of the differences between groups, we performed comparisons using the Student t-test and Fisher exact test. For variables with gaussian distribution, the values are presented as mean ± standard deviation and p was calculated using unpaired t-student test. Statistical significance was considered if $p<0.05$.

Results and discussions

The main finding of our work was that impaired RR variability, corelated with LP and Holter monitoring, is a good predictor for arrhytmic events as seen in table 2 and 3. URTI represents an independent prognostic marker for in-hospital morbi-mortality in patients with AMI. HRV was significantly lower in URTI group (table 2) , both in time domain standard deviation and also in frequency domain, maintaining up to 3 month of follow-up. Although there was a progressive improvement of HRV parameters for those with URTI, even at 3 months after URTI they remain at lower values when compared with non-URTI group (table 2). There was no statistical difference regarding the progression of late potentials.

The 24h Holter monitoring revealed the presence of systematised VEB during URTI (table 3). A larger number of patients from URTI group had a superior Lown class and the differences between the two groups were statistical significant as seen in table 3. All arrhythmic events were significantly more higher and more frequent during the URTI, including HRV variability in all of its aspects.

LP did not differ in incidence between the two groups, which means that the URTI din not affect the arrhythmic substrate, but precipitated its development. LP incidence is not influenced by fever, hypoxia or any other phenomenon. LP depend on the size of the infarct and have a negative predicted value on mortality and of life threatening ventricular arrhythmias. Factors that influence late potentials are: ischaemia, autonomous ischaemia and dyselectrolytemia. All these factors make the ischaemic myocardium vulnerable and can precipitate arrhythmias.

The small number of patients in our study and a short period of follow-up did not allow us to perform statistical analysis on mortality. Because URTI is very common and a normal person can have more than one episode per year, it is very difficult to estimate the exact burden of this disease during an acute coronary event or immediately after. Although a new infection is likely some time after, the majority of patients after AMI are more careful with respect to their health. In patients with known coronary disease, influenza vaccination is associated with a lower risk of cardiovascular events[14] and according to new guidelines we recomand annual influenza vaccination[15]. These results strengthen the importance of timely recognition of infectious complications in MI patients, which can be challenging given the overlap of RI and heart failure symptoms[16]. We did not analyse the etiology of the underlying pathogen that caused the URTI, but low grade fever and tachycardia increase the HRV imbalance and frequency of arrhythmic episodes. Respiratory infection recognition in myocardial infarction patients should promote the rapid institution of targeted therapy in order to minimise the deleterious effects of infection on myocardial function and recovery[17].

Parameter	URTI-AMI group N=54	Non-URTI AMI group N=52	p
HRV in TSD			
First week	28.01±4.68	43.18±6.95	< 0.0001
1 month	34.08±3.65	48.04±5.76	< 0.0001
3 months	46.32±7.54	52.83±6.06	0.001
HRV in HF			
First week	18.76±5.34	38.79±6.64	< 0.0001
1 month	24.39±6.85	44.48±6.95	< 0.0001
3 months	38.89±7.99	46.76±7.87	< 0.0001
LP presence			
First week	21(38.87%)	22(42.30%)	0.843
1 month	16(30.32%)	17(32.69%)	0.834
3 months	14(25.92%)	13 (25%)	1.000

Table 2
COMPARISION REGARDING RR VARIABILITY MEASUREMENTS AND LATE POSITIVE POTENTIALS

Ventricular arrythmia : Lown Grading System	URTI Holter group n=54	Non-URTI Holter group n=52	p
Class 0	-	19	0.0001
Class I	5	19	0.0026
Class II	14	5	0.0416
Class III (a+b)	14	4	0.0185
Class IV (a+b)	15	5	0.0243
Class V	6	-	0.0271

Table 3
PRESENCE OF VEB ACCORDING TO LOWN'S CLASSIFICATION IN 24H HOLTER MONITORING

Conclusions

URTI during subacute and late phase after MI increase the risk for life threatening arrhythmias. They decrease HRV and increases the myocardium electrial vulnerability. There were no differences in the temporal evolution of late potentials. URTI does not anatomically modify the electrophysiological substrate, but increase its susceptibility to any proarrhythmic stimulus. We suggest that acute upper respiratory infections during an acute coronary event should warrant immediate supportive treatment and a careful monitoring of potential hazardous arrhythmias.

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