Original Article

Physiological basis of therapeutic approach to ivabradine use in new acute onset heart failure

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Abstract

Background and Aim: Ivabradine is a selective and specific inhibitor of the sinus node funny current (I_f) channel with negative chronotropic properties while not affecting inotropy. Though the benefit of ivabradine in patients with coronary artery disease and chronic heart failure is well-established, data of its usage in acute heart failure (AHF) is scarce. We investigated the potential role of ivabradine in patients with acute ST elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention that postprocedurally present in hypoperfusion state without having complete criteria for cardiogenic shock, a state known as preshock or gray zone of cardiogenic shock, which is often associated with anterior STEMI and 46% in-hospital mortality.

Methods: During 2010, we conducted this pilot study on patients with acute STEMI where the culprit lesion was left anterior descending artery, complicated by the preshock. Altogether 10 patients (8 male and 2 female patients) were treated with ivabradine as an additional therapy who had stable sinus tachycardia. Their heart rate (HR), blood pressure (BP), degree of diuresis, and overall clinical response were recorded before and after ivabradine therapy.

Results: We observed a drop in HR from average 116−78/min, a rise in systolic BP from 99−108 mm Hg and a rise in diuresis from 55 to 85 mL/h within the first 48 h.

Conclusion: Early observational data support use of ivabradine in STEMI with advanced AHF. We propose that ivabradine could help STEMI patients in grey zone of cardiogenic shock (preshock).

Key words: Acute myocardial infarction, acute heart failure, ivabradine, pre-shock, primary angioplasty, ST elevation myocardial infarction

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INTRODUCTION

Ivabradine as a drug for the treatment of chronic heart failure (CHF) has been approved by European Medical Agency since 2005.[1] It is well-known for treatment of stable angina pectoris, which is included in the European Guidelines from 2006 as the class II A, level of evidence B, and endorsed in the 2013 Guidelines.[2] Ivabradine has negative chronotropic effect on heart both at rest and during exercise through its inhibitory effects on funny current (I_f) channel in the sinus node and has proven antiangina efficacy, for which it may be used as an alternative drug in patients who do not tolerate beta blockade.[1] Its only known pharmacological effect is to slow the heart rate (HR) in patients with sinus tachycardia and it does not slow the ventricular rate in atrial fibrillation. As ivabradine blocks the I_f channel that slows diastolic depolarization slope, it has no effect on left ventricular (LV) contractility and relaxation, cardiac conduction (atrioventricular or intraventricular), ventricular repolarisation, and blood pressure (BP).[3] Thus, cardiac effects of ivabradine are specific for the sinus node. The importance of HR reduction in relieving cardiac ischemia is well-documented, which has been implicated in the reduction of cardiovascular morbidity and mortality.[3] Trial of Systolic Heart Failure Treatment (SHIFT) was presented in 2010 that had

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enrolled 6588 patients in CHF. In SHIFT ivabradine was used in New York Heart Association (NYHA) functional classes II-IV patients, having sinus rhythm wih a rate of ≥70 b.p.m., and an ejection fraction (EF) ≤35%. These patients had hospitalization due to heart failure (HF) in the previous 12 months. They were randomized to ivabradine (uptitrated to a maximal dosage of 7.5 mg twice a day) group or placebo group, added to a diuretic (in 84%), digoxin (22%), an angiotensin-converting enzyme (ACE) inhibitor (79%), an angiotensin receptor blocker (ARB) (14%), a beta-blocker (90%), and a mineralocorticoid receptor antagonist (MRA) (60%). Only 26% of patients were, however, on full-dose beta-blocker. The median follow-up was 23 months. The relative risk reduction (RRR) in the primary composite outcome of cardiovascular death or HF hospitalization was 18% ($P < 0.0001$); the reduction in cardiovascular death (or all-cause death) was not significant, but the RRR in HF hospitalization was 26%. The absolute risk reduction in the primary composite mortality–morbidity endpoint was 4.2%. Ivabradine improved LV function and quality of life.[4] According to these results, ivabradine was included in European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic HF in 2012. Therefore, it has been suggested that ivabradine should be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF ≤35%, a HR remaining ≥70 b.p.m., and persisting symptoms (NYHA classes II-IV) despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and an MRA (or ARB).e – class II A, level of evidence B.[5-9]

However, there are very limited data on use of ivabradine in myocardial infarction (MI) and acute heart failure (AHF), though ivabradine seems to be a safe and potent drug in the management of AHF complicating acute MI with persistent ST-segment elevation.[10-13] The present study was designed to verify if ivabradine is safe and beneficial in the management of advanced form of AHF related to recovery process of anterior LV wall motion abnormality after primary percutaneous coronary intervention (PCI).

MATERIALS AND METHODS

Setting and participants

From January to the end of December 2010, we conducted a prospective study in our department of cardiology. ST-segment elevation myocardial infarction (STEMI) was defined according to the European Society of Cardiology/ American College of Cardiology by the presence of chest pain lasting at least 20 min not responding to nitrates, along with one of the following criteria: ST-segment elevation ≥2 mm in two or more electrocardiographic precordial leads or ST elevation ≥1 mm in two or more frontal leads, or left bundle branch block. Patients with an episode of chest discomfort within the previous 12 hours and ST-segment elevation, were included in the study. Coronary angioplasty was performed at the investigator's discretion using approved techniques and devices. Only the culprit vessel was targeted for primary PCI. Immediately after the diagnosis, the patients received a loading dose of 300 mg salicylic acid and 600 mg clopidogrel. During the procedure, they received 70 to 100 IE/kg of unfractionated heparin and, according to judgment of interventional cardiologist, a glycoprotein IIb/IIIa inhibitor. Postprocedural flow was classified according to the Thrombolysis in Myocardial Infarction (TIMI) grading system using a scale of 0 to 3. After primary PCI, the patients were hospitalized for an average of 2 to 3 days in the coronary care unit with continuous monitoring and treatment; however the patients with AHF stayed longer.[14-16]

In our study, we included patients with acute anterior wall MI after primary PCI on occluded left anterior descending artery (LAD) complicated by AHF with systolic arterial BP of 90-110 mm Hg, sinus tachycardia >110/min, and one of signs of hypoperfusion (oliguria, clouded sensorium, cold mottled skin, hypoxia, lactate >2 moll/L) a state described as preshock or ''gray zone of cardiogenic shock.''[16,17] The preshock is differentiated from cardiogenic shock which is defined as a clinical state of hypoperfusion characterized by a systolic BP of <90 mm Hg and/or a capillary wedge pressure of >20 mm Hg or a cardiac index of <1.80 L/min/m^2.[18,19]

The patients in preshock were administered ivabradine (uptitrated to a maximal dosage of 7.5 mg twice a day) in addition to the standard of care treatment for such patients. Exclusion criteria were heart blocks and any unstable ventricular or atrial arrhythmias. During their first hospital stay, general information (name, age, and gender) and data on the time of the first symptoms, time of arrival in the first hospital and/or PCI center, time of the first balloon insufflation during primary PCI, affected myocardial wall, and coronary artery, postprocedural flow, and, eventually, cardiogenic shock/preshock and lethal outcome, were collected. The median follow-up was 20 months. At 6 and 12 months after discharge, data on major adverse cardiovascular events and primary mortality were recorded for the investigated patients during their examination by checking the medical documentation or by telephonic interview with the patients, their family members, or home physicians. The institute ethics committee had approved the research protocol and the written informed consent was obtained from the subjects before starting the procedures.

Statistical analysis

Descriptive statistical analysis was performed in Microsoft Office Excel (2010). Values are presented as an absolute

value, as a percentage or as an average of multiple values. Analysis of statistical significance was performed using SPSS 13. The variation in the measured parameters at the time of admission and after 48 h of treatment with ivabradine in these patients was determined using Student's *t*-test.

RESULTS

During 2010, a total number of 384 patients with acute STEMI were treated with primary PCI. The criterion for cardiogenic shock was found in 20 patients (5.2%) and 28 patients (7.3%) presented as preschock (gray zone of cardiogenic shock) [Table 1]. In 42% of the all patients, the culprit lesion was LAD. We conducted this study in patients with acute STEMI in whom culprit lesion was LAD [Figure 1] and who were treated with primary PCI. Altogether, we enrolled 10 patients in stabile sinus rhythm (8 males and 2 females) with sinus tachycardia, hypotension, oliguria, and clinical signs of preshock. The majority of them besides acute STEMI suffered from three-vessel disease. At admission, all patients had systolic BP < 110 mm Hg, but had no profound hypotension. In all but one patient the BP increased after 48 h and we registered a rise in systolic BP from 99 to 108 mm Hg [Table 2]. This may not be the direct effect of ivabradine, but could be due to the improved hemodynamics attributed by more filling time.

Although, usually 50% of patients in gray zone of cardiogenic shock slip further into complete cardiogenic shock,[18-21] all of our patients improved, except only one died in hospital during follow-up after 6 months.

HR reduction was impressive from average 116/min to 78/min [Table 3]. Though reduction in HR cannot be completely attributed to ivabradine, the role of ivabradine in HR reduction is indisputable. In some instances, it reached 40% of initial HR.

Although not a strong parameter, we measured daily diuresis as a surrogate marker of improved hemodynamics. None of our patient was oliguric, but diuresis was expressed as average 24-h diuresis (which may blur the initially lower diuresis rates during the first 12 h or less) and we measured

Table 1: Percentage distribution of categories of shock in ST elevation myocardial infarction patients

Categories	No. of patients	distribution
STEMI	384	100%
Shock	20	5.2%
"Gray zone"- Preshock	28	7.3%

STEMI: ST elevation myocardial infarction

Table 2: Systolic blood pressure variation during the first 48 h of treatment

Patient Hospital no.	SBP (mm Hg)		
	Admission	Post 48 h	Delta difference
JH 1959	100	100	0
MR 1942	90	110	20
BL 1957	110	115	5
VC 1957	95	100	5
VF 1951	95	100	5
DB 1950	105	110	5
DB 1952	95	115	20
TA 1968	95	100	5
PS 1932	105	120	15
JS 1948	100	110	10
Average	**99**	**108**	**9**

Table 3: Heart rate variation during the first 48 h of treatment

Patient Hospital no.	Heart rate (1/min)		
	Admission	Post 48 h	Delta difference
JH 1959	115	81	34
MR 1942	111	92	19
BL 1957	116	86	30
VC 1957	124	77	47
VF 1951	115	76	39
DB 1950	111	64	47
DB 1952	119	72	47
TA 1968	121	72	49
PS 1932	111	79	32
JS 1948	117	81	36
Average	**116**	**78**	**38**

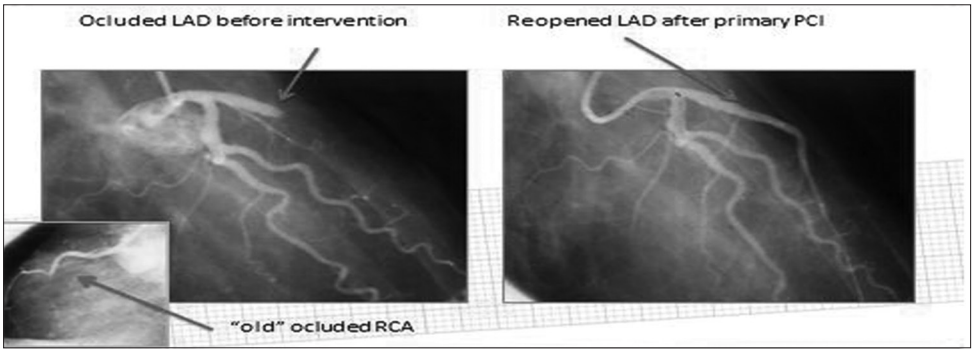

Figure 1: Patient VC 1957 with previous inferior myocardial infarction and "new" anterior ST elevation myocardial infarction who developed preshock after primary percutaneous coronary intervention (PCI)

a rise in diuresis from 55 to 85 mL/h within the first 48 h [Table 4]. All patients showed improved systolic BP, HR, and rate of diuresis after the 2nd day of treatment [Table 5].

DISCUSSION

According to SHIFT and BEATIFUL (mor**B**idity-mortality **E**v**A**lua**T**ion of the **IF** inhibitor ivabradine in patients with coronary disease and left ventric**UL**ar dysfunction) trials, elevated HR is associated with poor outcome in a number of cardiovascular conditions including HF. HR remains elevated in many HF patients despite the treatment by beta-blockers. The authors of two studies hypothesized that the addition of ivabradine to a recommended therapy would be beneficial in CHF patients with elevated HR (sinus tachycardia).[4,5,22] But, nothing is conclusive in AHF. In our study, AHF was defined as a rapid onset or change in the signs and symptoms of HF, resulting in the need of urgent therapy as new onset HF. Multiple cardiovascular and noncardiovascular morbidities may precipitate AHF that is commonly a direct result of myocardial injury caused by the underlying ischemia or infarction.[6] Ivabradine seems to be a safe and potent addition in the management of AHF complicating acute MI. Because of the complexity and diverse nature of the acute HF syndrome, the treatment should be individualized. In these cases, if an appropriate treatment is not instituted within a reasonable period, irreversible cardiac decompensation may ensue, leading to a progressive syndrome of shock, multiorgan failure, and death. Despite the efficacy of early reperfusion with PCI for preventing shock, there has been no change in nearly 8% incidence of cardiogenic shock.[21]

Table 4: Diuresis variation during the first 48 h of treatment

Patient Hospital no.	Diuresis (mL/48 h)		
	Admission	Post 48 h	Delta difference
JH 1959	40	81	41
MR 1942	42	92	50
BL 1957	52	86	34
VC 1957	32	77	45
VF 1951	73	92	19
DB 1950	77	101	24
DB 1952	40	72	32
TA 1968	55	72	17
PS 1932	59	79	20
JS 1948	80	99	19
Average	**55**	**85**	**30**

Table 5: Variation observed during the first 48 h of ivabradine treatment (*n*=10)

Parameters	On admission	Post 48 h	*P* value
Systolic blood pressure	99±6.15	108±7.53	0.009
Heart rate	116±4.42	78±7.83	<0.001
Diuresis	55±17.15	85 ±10.57	<0.001

Data are expressed as mean±standard deviation. Statistical analysis was done by unpaired *t* test

There are reports that patients who develop delayed cardiogenic shock following MI usually slip into shock slowly, with evidence of a low cardiac output clinically before the onset of hypotension.[18,23,24] Sympathetic stimulation may result in maintenance of normal BP in patients with high systemic vascular resistance and low cardiac output. The preshock or nonhypotensive shock state is associated predominantly with anterior MI and a 46% in-hospital mortality in the SHOCK (SHould we emergently revascularize Occluded Coronaries in cardiogenic shocK?) Trial Registry.[21] Sinus tachycardia and low urine output are clinical findings of reduced stroke work and cardiac output. It must be appreciated that these signs reflect severe depression of cardiac output and necessitate rapid evaluation of patients before the onset of frank hypotension. When severe LV dysfunction leads to reduction in stroke work, high HR is necessary to maintain cardiac output. In general, HR of approximately 90-100/min are advisable in these patients. We wonder if there is any reason why patients in gray zone of cardiogenic shock (preshock) with HR over 100 beats per minute, should be administered ivabradine in addition to standard medication? As we know these patients are exposed to overaccentuated sympathetic stimulation and with HR over 100 beats per minute, they have a relative contraindication for inotropic stimulation with sympathomimetic agents. Elevated HR (>70/min) is a strong predictor of morbidity and mortality in a number of cardiovascular disorders including coronary artery disease and CHF.[3] Therefore, use of ivabradine for controlling HR will be an appropriate therapeutic measure for the treatment of AHF in STEMI patients.

CONCLUSION

The cardiac effect of ivabradine is specific to the sinus node. This study demonstrated ivabradine to be safe and potent not only in CHF, but also in advanced AHF with preshock complicating myocardial infarction. Ivabradine, in addition to conventional therapy without intravenous inotropic stimulation with sympathomimetic agents, improves short-term outcomes in those patients. Out of 10 patients, only one died. The sample size was small in the present study to estimate mortality benefits. However, no adverse effect of ivabradine was detected. Ivabradine being a pure HR-reducing agent, findings of the present study demonstrate the therapeutic usefulness of ivabradine in AHF of STEMI patients especially if they are in the gray zone of cardiogenic shock (preshock). For further evaluation, a randomized controlled trial may be required to confirm the outcome of this preliminary study.

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