

Myocardial Ischemia Presenting with Hiccups

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ABSTRACT

Myocardial infarction/ischemia can be an underlying etiology and a major causative risk factor of cardiovascular hiccups. The objective of this systematic review was to review the literature regarding clinical features and treatments of hiccups of cardiac ischemia origin. PRISMA guidelines were followed. In elderly patients with hiccups of uncertain causes, electrocardiography is necessary to ensure the cardiogenic etiology. Both symptomatic and etiologic treatments can be effective in terminating hiccups. Of the therapeutic regimens, gabapentin is a second-line agent alternative to baclofen in treating hiccups. It is especially helpful in patients undergoing stroke rehabilitation or palliative care when chlorpromazine is prohibited due to its adverse effects. Inferior myocardial infarction is the most common cause of hiccups in this patient setting. In addition to anti-myocardial ischemia agents and percutaneous coronary intervention, coronary artery bypass grafting could be an alternative to hiccups in such patients.

Key Words: *Hiccup, Myocardial infarction, Treatment outcome, Myocardial ischemia.*

INTRODUCTION

The description of cardiovascular hiccups could be dated back to the 1930's, when it was known that hiccups could be induced by several cardiovascular disorders including thoracic aorta aneurysm, coronary artery occlusion, cardiac surgery, congestive heart failure, and even heart enlargement.¹ However, the concept of cardiovascular hiccups did not appear until 1993 when Launois *et al.* comprehensively reviewed hiccups in adulthood.² Cardiovascular hiccups may be divided into cardiogenic, vasogenic, iatrogenic, and pharmacogenic. Clinical observations demonstrated that acute myocardial infarction (AMI) was the most common cause of cardiogenic hiccups. Hiccups as a primary or an only presentation of AMI might be misdiagnosed as gastrointestinal disorders in many occasions. Clinical features of the hiccups induced by myocardial infarction/ischemia remain unclear, and relationships between hiccup onset and myocardial infarction/ischemia have not been evaluated.

This study aimed to disclose clinical features of myocardial infarction/ischemia-induced hiccups.

METHODOLOGY

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement guidelines were followed in this meta-analysis.³ Publications were

systematically searched in the PubMed, Highwire Press, and the Cochrane Library databases until August 2018. The MeSH terms and keywords used to identify articles included myocardial ischemia, myocardial infarction, angina pectoris, and hiccup / hiccough / singultus / eructation / belching / burping. Screening of the bibliographic references helped in completing the literature retrieval. Forty-seven articles were found related to the topic and keywords in the literature search; and 25 articles, which met the inclusion and exclusion criteria during preliminary assessment, were included in the review. Exclusion criteria were literature not relevant to myocardial infarction/ischemia and hiccups (n=11), background discussion of myocardial infarction/ischemia or hiccups (n=8), hiccups induced by disorders other than myocardial infarction/ischemia (n=2), and no substantial patient information available (n=1).

The data independently extracted from each study were study population, demographics, natures of hiccups, regions of myocardial infarction/ischemia, onset time of hiccups, symptom duration, treatments, therapeutic effects, and outcomes. Hiccups can be divided into bouts (occasional), persistent (lasting >2 days), and intractable (lasting >1 month).⁴

Data analysis was based on the Cochrane Collaboration and the PRISMA Statement. The measurement data were expressed in mean \pm standard deviation. The categorical variables expressed by n (%) were compared by Fisher exact test. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 129 patients were involved in the 25 articles,⁵⁻²⁹ including 5 original articles,^{8,10,12,21,27} and 20 case reports.^{5-7,9,11,13-20,22-26,28,29} There were 37 (67.3%) males and 18 (32.7%) females with a male-to-female ratio of 2.1:1. Patients' ages were 65.5 ± 6.4 years (n=22). Seventeen (77.3%) patients were <70 years, and five (22.7%) patients were >70 years ($\chi^2=13.09$, $p=0.001$).

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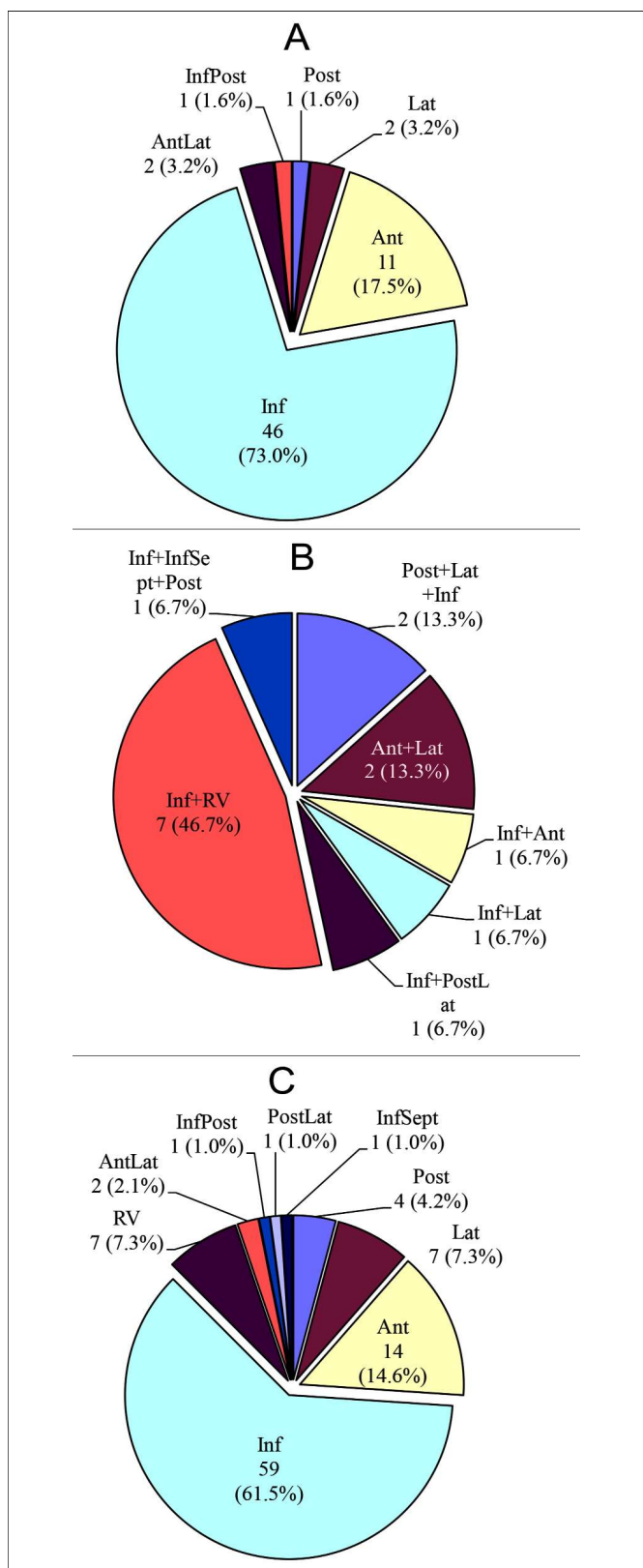


Figure 1 : Distribution of the regions of myocardial infarction/ischemia as a cause of hiccups in patients with myocardial infarction/ischemia: **(A)** single wall region involvement; **(B)** multiple wall region involvements; and **(C)** counting on each region by incorporating both single and multiple region involvement cases.
 Ant: anterior; AntLat: anterolateral; Inf: inferior; InfPost: inferoposterior; InfSept: inferoseptal; Lat: lateral; Post: posterior; PostLat: postlateral; RV: right ventricle.

The underlying etiology was myocardial infarction in 127 (98.4%) patients,^{5,7-17,19-25,26-29} and myocardial ischemia in 2 (1.6%) patients.^{6,18} Of the myocardial infarction group, one patient each was diagnosed with Dressler syndrome,¹⁶ associated with ischemic cardiomyopathy and atrial fibrillation,¹⁵ and had in-stent thrombosis of the right coronary artery.²⁹ In one patient, myocardial infarction was chronic with a 4-year medical history,¹⁵ and another patient had a 2-year history of myocardial infarction with an acute onset at current presentation.²⁶ Except for these two patients, all remaining patients had AMI. One patient with myocardial ischemia showed electrocardiographically atrioventricular dissociations.⁶

The regions of myocardial infarction/ischemia were reported in 78 (60.5%) patients: 63 (80.8%) patients,^{5-7,9,10,12,17,19,21,24,26,27,29} had single region involvements and 15 (19.2%) patients,^{7,8,14,16,18,23,28} had multiple region involvement ($\chi^2=59.08, p<0.001$).

In total, there were 96 involved regions (mean, 1.2 regions/patient). The inferior wall was the region most commonly involved by myocardial infarction/ischemia in patients with single myocardial region involvement (Figure 1A), and the inferior wall plus right ventricle involvement was the myocardial region most commonly involved in the multiple region group (Figure 1B). When counting on each single region by incorporating both single and multiple region involvements, the inferior wall was the most commonly involved region (Figure 1C).

The duration of hiccups was recorded in 18 (14.0%) patients. In one patient, it was described as several weeks.²⁵ In the remaining 17 patients, the hiccup duration was 15.4 ± 64.3 (range, -7~240; median, 1.5) days. For patients with AMI or acute myocardial ischemia, the hiccup duration was recorded as a minus when hiccups occurred post-admission.^{5-8,10,12,14,16,17,19-21,27} It was 1,460 days (4 years, n=1) for the patients with chronic myocardial infarction.¹⁵ The situation of hiccups among other symptoms was described in 21 (16.3%) patients: hiccups as an only presentation of myocardial infarction in 7 (33.3%) patients,^{5,10,12,14,21,27} as a primary symptom in 8 (38.1%) patients,^{6-8,15,20,23,29} and as an accompanying symptom in 6 (28.6%) patients.^{13,16-19,26}

Hiccups could be defined according to Thompson and Brooks' classification in 21 (16.3%) patients: Hiccups were persistent in 15 (71.4%) patients,^{5-8,12,14,17,18,21,23,26,27} and intractable in 6 (28.6%) patients,^{10,13,15,19,20,29} ($\chi^2=7.71, p=0.013$). In two patients, persistent hiccups were recurrent, induced by exertional effort.^{7,18} Seven patients did not have a chest pain.^{5,6,10,12,23,27,29} In three patients, chest pain and hiccups occurred simultaneously.^{7,18} The time intervals between the onset of myocardial infarction and that of hiccups were available for 7 (5.4%) patients, showing that hiccups occurred 3.7 ± 0.7 days after myocardial infarction (n=6).^{14,16,17,19,20,26}

Table I: The treatment of choices for the hiccups with different therapeutic effects.

Treatment of choice	Ineffective	Minimal effect	Effective
Non-pharmacological	Maneuvers ¹⁷ Oxygen ²³ 5% CO ₂ ^{14,17} Breath-holding ¹⁹ Continuous positive airway pressure ¹⁹	Homeopathic products	Acupuncture [GV14 (Dazhui)] ¹⁹
Pharmacological			
<i>Agents against psychiatric disorders</i>	Chlorpromazine ^{5,10,12,14,19,20} Metoclopramide ¹⁹ Prochlorperazine ¹⁹ Haloperidol ¹⁹	Metoclopramide ¹⁵	Chlorpromazine ²³ Triflupromazine ¹⁵
<i>Antiparkinsonian agent</i>		Levodopa ¹⁵	
<i>Anticonvulsant</i>	Diphenylhydantoin ¹⁹ Phenobarbital ¹⁹		
<i>Antianxiotic</i>			Clonazepam (0.5 mg, twice daily) ²⁰ Gabapentin ¹⁵
<i>Antiepileptic, anticholinergic agent</i>	Belladonna ⁶ Atropine ⁶ Ativan ¹⁰		
<i>Antiemetic</i>			Dimenhydrinate (25 mg, trice daily) ²⁰ Xylocaine (phrenic nerve blocking) ¹⁴
<i>Anaesthetic</i>			
<i>Prokinetic agents</i>	Domperidone ⁸ Metoclopramide ²⁰	Digestive enzymes ¹⁵	
<i>Muscle relaxant</i>	Baclofen ^{19,20} Mephennesin ¹⁹		Baclofen 5 mg ²⁵
<i>Cardiovascular drugs</i>	Coagulant ^{5,16} Aspirin ²³ Nitroglycerin ²³ Quinidine ⁶		Aspirin ^{10,21,23} Clopidogrel ^{10,21} Heparin ^{10,21,23} Atorvastatin ²¹ Simvastatin ²³ Metoprolol ^{21,23} Digoxin ¹³ Neosynephrine ¹³ Amiodarone ²³ Procainic amide ⁶ Prednisolone ^{12,16} Percutaneous coronary intervention ^{7,18} Phrenic nerve crush ²⁶
<i>Glucocorticoid</i>			
Interventional			

Table II: A comparison of the prognosis between etiologic and symptomatic treatment patients.

Treatment	Cured / improved n (%)	Self-cured n (%)	Recurrent n (%)	Died n (%)
Type of hiccup				
Persistent	10 (71.4)	2 (14.3)	0 (0)	2 (14.3)
Intractable	4 (66.7)	0 (0)	1 (16.7)	1 (16.7)
χ ²	0.045	0.952	2.456	0.000
p-value	1.000	1.000	0.300	1.000
Treatment of choice				
Etiologic	9 (90)	0 (0)	0 (0)	1 (10)
Symptomatic	6 (60)	2 (20)	1 (10)	1 (10)
χ ²	2.400	2.222	1.053	0.000
p-value	0.303	0.474	1.000	1.000

The timing of treatment of hiccups was 20.8 ±13.8 days (n=14) after hiccup onset in AMI or acute myocardial ischemia patients,^{5-8,10,12,14,16,21,29,26,27} and 4 years after

chronic myocardial infarction.¹⁵ It was 1.1 ±0.5 days after current presentation/admission (n=14).^{5,6,8,10,12,14-16,21}

The initial therapeutic attempts failed in 13 (10.1%) patients for 11.3 ±5.7 days (n=9).^{4,5,7,9,11,13,15,18,25} The effective therapeutic regimens by medications were reported in 8 patients for 19.2 ±40.9 days (n=8).^{6,10,12,14-16,20,21} The agents with minimal effects for hiccups were also reported with the use of metoclopramide, triflupromazine, levodopa, digestive enzymes, and homeopathic products.¹⁵ The effects of different therapeutic treatments are shown in Table I.

The timing for the medical regimens to take effect was 0.5-1 days.^{6,10,12,14,19,21} The cure-time was 17.2 ±38.7 days (n=9).^{6,10,12,14-16,19-21} With the treatment, the hiccups lasted 15.6 ±16.3 days (n=11) until hiccups were cured or improved in AMI or acute myocardial ischemia

cases,^{5,6,8,10,12,14,16,19,21,23,25} It lasted 1,580 days (4.5 years) for the patient with chronic myocardial infarction.¹⁵

Treatment of choices was described in 21 (16.3%) patients: 12 (57.1%) patients received an etiologic treatment with anti-myocardial ischemia agents or percutaneous coronary intervention.^{6,7,10,12,13,16,18,21,23,27,29} Nine (42.9%) patients received symptomatic treatment.^{5,8,14,15,19,20,25,26} One patient died suddenly before proper treatment was started.¹⁷ The outcomes under treatment were available for 23 patients: 16 (69.6%) patients were fully recovered,^{4,6,8,10,13,14,16,18-21,25,27} two (8.7%) patients were self-cured,^{5,8} one (4.3%) patient improved,¹² one (4.3%) patient underwent recurrent hiccups,¹⁵ and three (13.0%) patients died (including a recurrent case with a death cause unrelated to hiccups).^{15,17,23} No significant differences were found in the outcomes between etiologic and symptomatic treatment patients, and in the curative and self-cure rates between patients with persistent and intractable hiccups (Table II).

DISCUSSION

There were some disparities regarding time limit definition for hiccup classification. Thompson and Brooks⁴ defined transient, persistent, or chronic hiccups as lasting for <1 day, <2 days, and >1 month. However, Jatzko *et al.* defined hiccups as transient (acute), <1 day; persistent, <1 week; and chronic, >1 week.¹⁵ It is certain that different classifications would surely influence the statistical results of the study. In this report, Thompson and Brooks' classification was followed.

Culic *et al.* studied the relationship between symptomatology and myocardial infarction regions and found that hiccups accounted for 5.3%, 2.1%, and 1.1% of the inferior, lateral, and anterior wall infarctions, respectively.⁹ They concluded that inferior infarctions were more likely to induce hiccups, nausea, and vomiting. Pasceri *et al.* analysed the relationship in 104 patients with AMI, and reported that all four hiccup patients were with inferior AMI and no patients were with anterior wall AMI.²⁴ Sinha *et al.* observed nine patients with AMI had hiccups, seven of whom had inferior wall plus right ventricle AMI and two had purely inferior wall AMI.²⁸ Hiccups were seen more often in patients with inferior wall myocardial infarction compared to infarctions of other territories.⁹ This may be because the vagal fibers of cardiac plexus are within the inferoposterior myocardium and phrenic nerve, which provide motor fibers to the diaphragm and sensory branches to the pleura and pericardium. The irritation from the infarct or ischemia area may result in stimulation of these fibers and cause hiccups. Therefore, physicians shall consider extension of infarction to the inferior wall if a patient with an otherwise stable myocardial infarction develops hiccups.³⁰

The etiologic diagnosis of hiccups in patients with myocardial infarction/ischemia can be challenging, as

chest pain is absent in one-third of the patients. In those with exertional effort-induced hiccups, a diagnosis of myocardial ischemia should be considered.¹⁸ This study reveals that myocardial infarction/ischemia may induce persistent or intractable hiccups four days after myocardial insult in patients at the sixth decade of age. Therefore, in elderly patients with hiccups of uncertain causes, electrocardiography is necessary to ensure the cardiogenic etiology.

Of the therapeutic regimens, gabapentin was praised as a second-line agent alternative to baclofen in treating hiccups. It is especially helpful in patients undergoing stroke rehabilitation or palliative care when chlorpromazine is prohibited due to its adverse effects.⁵ Petroianu *et al.* recommended the combination of cisapride, omeprazole, and baclofen as an effective empiric therapy for patients with persistent hiccups unresponsive to gabapentin and baclofen.³¹ Meanwhile, chlorpromazine use should be cautious in coronary patients with hiccups, if the patients are hypotensive.¹⁴

This study shows that both symptomatic and etiologic treatments might be effective in terminating hiccups. Since anti-myocardial ischemia agents and percutaneous coronary intervention could effectively cease hiccups, it is anticipated that coronary artery bypass grafting could also be an alternative to hiccups in such patients.

The smaller patient population and lack of necessary information of the patients were the two main drawbacks of this study. More acute results, based on more abundant variables with large patient populations in the near future, are anticipated.

CONCLUSION

Myocardial infarction/ischemia-induced hiccups are rare, etiologic diagnosis can be challenging and cause delayed diagnosis. The characteristic exertional effort-related hiccups might raise the suspicion of a myocardial infarction/ischemia origin. Myocardial infarction/ ischemia may cause hiccups about 4 days after myocardial insult in patients at sixth decade of age. Inferior myocardial infarction is the most common cause of hiccups. Additionally, both symptomatic and etiologic treatments can be effective in terminating hiccups. The curative rates were similar for persistent hiccups and for intractable hiccups. In addition to anti-myocardial ischemia agents and percutaneous coronary intervention, coronary artery bypass grafting could be an alternative to hiccups in such patients.

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