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CONTENT

Int J Cardiovasc Pract. **Review Article**

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Updates on Advanced Therapies for Acute Pulmonary Embolism

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Abstract

Venous thromboembolism is the third common vascular disease after acute myocardial infarction and stroke, and acute pulmonary embolism (PE) remains as the most common preventable cause of in-hospital mortality. In addition to routine anticoagulant therapy, several advanced treatment options have been introduced over the past three decades. We provide a succinct and contemporary summary of the evidence base and important indications for inferior vena caval filter placement, systemic and catheter-based thrombolytic therapy, as well as percutaneous and surgical thrombectomy. Appropriate case selection for advance therapies for PE could minimize the adverse effects and costs, while optimizing the outcomes.

INTRODUCTION

Acute pulmonary embolism (PE) is a common and potentially lethal medical condition. Annually, there are an estimated 1,000,000 cases of PE in the Western countries [1, 2]. Thirty-day mortality rates have been variably reported between 6-9% in contemporary registries, and up to as high as 50% in patients with massive PE, defined by development of systemic hypotension [3-5]. Beyond systemic anticoagulation, advanced treatment approaches have opened their way in several subgroups of patients with PE. Such options include inferior vena caval (IVC) filters, thrombolytic therapy (with or without ultrasound facilitation), and surgical or percutaneous thrombectomy. Here, we provide a succinct review of the latest evidence and recommendations relating to advanced treatments for acute PE.

IVC Filters

A recent analysis of Medicare beneficiaries > 65 years old demonstrated that roughly 17% of patients hospitalized with a PE, an unexpectedly high proportion, received an IVC filter [6]. Such findings are particularly striking taking into consideration the limited available evidence for efficacy of IVC filters.

So far, there have only been two major randomized controlled trials published on the use of IVC filters [7, 8]. The PREPIC trial, an open-label study of 400 patients with proximal deep vein thrombosis (DVT) randomized to IVC filter placement plus anticoagulation versus anticoagulation alone did not show a mortality difference between the two groups at 2-year or 8-year follow-up, and the reduced rates of PE in the study were counterbalanced by increased rate of recurrent DVT [7-9]. With technological advances, such as introduction of retrievable filters (that would have potentially mitigated the increased risk of recurrent DVT below the filter), use of IVC filters continued to grow despite the dearth of clinical evidence for improved outcomes. In recent years, results of the PREPIC II trial, an open-label study of 400 patients hospitalized with acute symptomatic PE with concomitant lower extremity DVT and at least one feature increasing the risk of PE recurrence, who were randomized to anticoagulation alone versus anticoagulation plus (retrievable) IVC filters, became available. At 3-month follow-up, the study did not detect a difference in mortality rates, and reported statistically similar but numerically higher rates of PE in patients who did receive an IVC filter [10]. Several other recent studies have also shown that many patients have received IVC filters in scenarios other than those recommended by the expert guidelines [11].

In summary, the overall existing evidence for the use of IVC filters is quite limited, and these devices should only be used as a last resort once there is no other evidence-based option available. Expert guidelines recommend against use of IVC filters as a routine treatment for acute PE. The limited reasonable indications for IVC filter placement would

include contraindication to anticoagulant therapy [12], and recurrent events despite adequate anticoagulation (i.e. recurrence despite anticoagulation with good adherence and objective evidence of therapeutic anticoagulant levels). There is no consensus for use of IVC filters in other scenarios, such as presence of poor cardiopulmonary baseline reserve, or in the case of massive PE.

Systemic Thrombolytic treatment

Along with the conceivable benefits of thrombolytic therapy for an acute thrombotic condition such as PE comes the cost in the form of bleeding events, with the absolute risks increasing by increased age, including that of intracranial hemorrhage, the most feared bleeding complication of thrombolytics. Appropriate use of thrombolysis is associated with more rapid resolution of symptoms, cardiorespiratory (hemodynamic) stabilization, improvement in right ventricular function, improved exercise tolerance, prevention of PE recurrence, and according to a recent systematic review of the literature (predominated driven by the PIETHO trial participants), improved survival [13-16].
Increased risk of bleeding is well known with thrombolytic therapy, especially among older adults. Yet, the benefits of thrombolytic therapy among older adults are frequently underrated [17] while the risk of bleeding from thrombolysis in elderly PE patients is traditionally exaggerated; although this idea has been challenged in several recent studies [18-20]. Nevertheless, several studies suggest that use of thrombolytic therapy is rare in older adults [18, 21].
Use of ultrasound-facilitated thrombolysis emerged as a fascinating option in recent years, which was associated with an excellent safety profile in a small randomized trial and a prospective single arm study of patients with sub-massive or massive PE. The improved safety profile is likely due to lower dose of thrombolytics (up to a quarter of regular systemic dose) and administration over 12-24 hours according to various protocols, as opposed to bolus administration of regular systemic thrombolytics [22, 23]. Reduced-dose systemic thrombolytic therapy has been also successfully tried in a small study of patients with "moderate PE" (defined as computed tomographic pulmonary angiographic evidence of involvement of > 70% in ≥ 2 lobar or left or right main pulmonary arteries) [14].
Massive PE, i.e. PE along with hemodynamic instability, represents the clearest indication of thrombolytic therapy. Risks and benefits of thrombolytic therapy in patients with non-massive PE should be seriously considered (Fig 1). While reduced-dose thrombolysis could be reasonable in a select group of patients with sub-massive (or even moderate) PE, routine use of thrombolytic therapy in all-comers with PE is not recommended.

Catheter Directed Treatments Other Than Thrombolytic Therapy

Catheter directed treatment may refer to any or a combination of catheter directed thrombectomy, catheter directed fragmentation and catheter directed thrombolysis. Catheter-directed thrombolytic therapy could be performed alone, or in conjunction with thrombus aspiration using catheters such as the regular 8F guide catheters [24]. Several other percutaneous thrombectomy devices are also under early investigation, and at least one of them (the AngioVac Cannula) has received FDA approval for removal of detrimental intravascular material, such as soft thrombi [24].

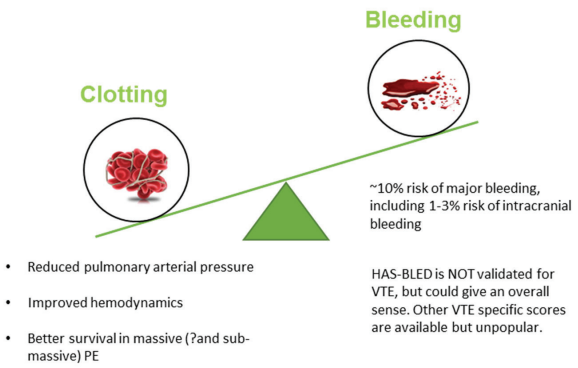

Figure 1: Risks and Benefits of Thrombolytic Therapy in Patients with PE

Surgical Thrombectomy

Surgical embolectomy, a procedure that requires much expertise and is performed under cardiopulmonary bypass, occurs only in very experienced centers. In patients suffering from massive PE who have contraindications to, or are not good candidates for thrombolytic therapy, and have a reasonable operative risk, surgical thrombectomy, with or without extracorporeal membrane oxygenation (ECMO) could be life-saving. However, because of the extreme level of illness of such patients, conducting high-quality prospective comparative effectiveness in such patients has not been yet feasible. Data from the US indicates a declining trend for utilization rates of surgical thrombectomy, likely as a result of more widespread availability of other advanced therapies [21].

CONCLUSIONS

With new emerging evidence for more aggressive treatment of PE with potentials for decreased mortality and long-term morbidity, it appears that options for PE treatment will broader in future. Prior to choosing advanced therapies, however, risk stratification would be crucial. The concept of a pulmonary embolism response team (PERT) is now growing in several centers around the world and might help improve decision-making for the choice and timeliness of PE advanced therapies, where needed. With wise use of PERT teams, collaborative interdisciplinary efforts, and other initiatives to raise the awareness for optimal diagnosis and treatment of PE we can aim to reduce the burden of venous thromboembolism, one of the most common and yet underappreciated cardiovascular conditions.
Careful consideration of benefits and risks is key, particularly for patients with hemodynamically-stable PE who have other features of increased risk of adverse events. Risks of hemorrhagic complications should be particularly weighed in the case of older adults. Reduced-dose thrombolytics are a fascinating option with a seemingly better safety profile and currently under intense investigation (Table 1).

Table 1: Summary of Select Indications for Advanced Therapies for Acute PE

	Therapies
Inferior Vena Caval (IVC) Filters	
Acute PE with clear contraindications to anticoagulant therapy	IVC filter placement is reasonable
Recurrent PE despite adequate anticoagulant therapy	IVC filter placement is reasonable
Acute PE with poor cardiopulmonary reserve, including massive PE	IVC filter placement might be considered in select cases.
Acute hemodynamically-stable PE in patients tolerant of anticoagulants	IVC filter placement is not recommended.
Thrombolytic Therapy	
Massive PE (hemodynamic instability not attributable to other factors)	Thrombolytic therapy is recommended
PE with elevated cardiac biomarkers and imaging evidence of right ventricular dysfunction	Thrombolytic therapy (preferentially low-dose or ultrasound-facilitated) may be considered in select cases.
Hemodynamically stable PE without evidence of biomarkers rise and right ventricular dysfunction (all-comers with acute PE)	Thrombolytic therapy is not recommended.
Catheter Directed Therapies Other Than Thrombolysis	
Acute severe PE (large burden, clot in-transit)	Catheter directed techniques (e.g. aspiration/ thrombectomy) might be considered in experienced centers for select cases.
Surgical Thrombectomy	
Acute massive PE and acceptable surgical risk	Surgical thrombectomy should be considered in cases of acute massive PE in highly experienced centers.
Acute severe PE (large burden, clot in-transit)	Surgical thrombectomy might be considered in select cases of large burden PE in highly experienced centers.
Acute hemodynamically-stable PE (all-comers with acute PE)	Routine use of surgical thrombectomy is not recommended.

Use of a multidisciplinary Pulmonary Embolism Response Team (PERT) can help facilitate the selection of advanced therapies in each case.
Abbreviation: IVC, inferior vena caval filter; PE, pulmonary embolism.

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None declared.

CONFLICTS OF INTEREST

There is no conflict of interest.

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Int J Cardiovasc Pract. **Original Article**

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One- and Six-month Outcomes of Patients with Non-ST Elevation Myocardial Infarction

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Abstract

Introduction: Use of risk scoring systems in patients with acute coronary syndrome helps with summarizing important prognostic data of the disease and facilitates calculating confidence limits and comparing survival rates between different treatments. In the present study, the researchers first aimed at assessing mid-term outcome of patients with non-ST elevation myocardial infarction (NSTEMI), and then determining main predictors of this outcome to improve definitive criteria for designing a risk scoring system in the population.
Methods: In a prospective cohort study, 124 patients with NSTEMI, diagnosed according to ACC/AHA guidelines and hospitalized in an academic hospital in 2013, were consecutively assessed. Baseline characteristics were collected via interviewing, physical examination, and reviewing the recorded files. All the patients were followed for one and six months to assess mid-term outcomes regarding mortality and major adverse cardiac events (MACE). MACE is defined as the occurrence of at least one of the events of death, myocardial infarction, repeated revascularization, or re-hospitalization.
Results: One-month death occurred in 3.2%, re-hospitalization in 4.0%, and myocardial infarction in none of the patients. In addition, regarding the six-month outcomes status, mortality rate was determined in 6.4%, re-hospitalization in 22.6%, and myocardial infarction in 4.8% of patients. Hence, one- and six-month MACE rates were 7.3% and 27.4%, respectively. Furthermore, three- and six-month survival rates were estimated to be 96.8% and 93.6%, respectively. According to the Cox-proportion hazard modeling, only reduced left ventricular ejection fraction (LVEF) (HR = 0.909, P = 0.017), history of chronic kidney injury (HR = 8.884, P = 0.005), and Inotrope use (HR = 35.759, P = 0.012) could predict the six-month MACE. None of the other indexes including general coronary risk factors, echocardiography parameters, and level of cardiac enzymes could predict mortality rate.
Conclusions: Patients with NSTEMI may face high six-month MACE which can be predicted by low LVEF, history of renal injury and use of inotrope. Therefore, to define risk stratification system, these indicators should be considered as well.

INTRODUCTION

The ratio of non-ST elevation myocardial infarction (NSTEMI) to ST elevation myocardial infarction (STEMI) continues to increase, and now less than one-third of myocardial infarctions (MIs) are due to STEMI [1]. Recently, the wide use of more sensitive tests such as analyzing serial high-sensitivity cardiac troponin T (hs-cTnT), which can detect even small sizes of myocardial necrosis, has increase diagnostic accuracy and led to increasing incidence of NSTEMI instead of unstable angina [2-5]. Although there have been significant improvements in the care of patients with cardiovascular disease, cardiovascular death mainly by coronary heart disease remains the leading cause of mortality worldwide [1]. Risk scores are simple, applicable and more accurate tools at risk stratification, in which prognostic value of several independent risk factors on presentation are shown. Indexes that compound several related clinical variables of

the same underlying pathophysiologic event are more powerful than any individual variable and could improve prognostic analysis in regression modeling techniques [6-8]. For instance, history of myocardial infarction, congestive heart failure, Q waves on electrocardiogram and high troponin T concentrations all represent different aspects of the extent of myocardial injury [9, 10]. In addition to the extent of myocardial injury, the extent of coronary artery disease and its resistance to management are the main prognostic determinants of acute coronary syndrome [11].

Age, heart rate, systolic blood pressure, Killip class, ST segment deviation, resuscitation from cardiac arrest, elevated cardiac enzymes and serum creatinine concentration are powerful prognostic factors in GRACE and PURSUIT scoring systems [12-14].

Seven independent predictor variables have been identified as TIMI risk factors including age > 65 years, three cardiovascular risk factors, known coronary artery disease (50% stenosis), severe angina symptoms, use of aspirin in the last seven days, ST segment deviation > 0.05 mV, and elevated serum cardiac markers of necrosis [15, 16]

Use of risk scoring systems in patients with acute coronary syndrome helps to summarize important prognostic data of the disease and facilitates comparing survival rate between different treatments [17, 18].

In the present study, we aimed to first assess mid-term outcome of patients with NSTEMI, and then determine main predictors of this outcome.

METHODS

In a prospective cohort study, 124 patients with diagnosed NSTEMI according to ACC/AHA guidelines, who were hospitalized at Modarres hospital between March 2012 and September 2013, were consecutively included. Baseline characteristics were collected via interviewing, physical examination, and reviewing the recorded files including demographic characteristics, medical history, medication, previous cardiac intervention, laboratory parameters, and functional class status.

Patients were also assessed using two-dimensional echocardiography to determine structural and functional parameters such as left ventricular ejection fraction, end systolic and diastolic diameters, and also diastolic functional indexes. They also underwent coronary angiography to determine presence and severity of coronary arteries involvement.

To assess mid-term outcomes of NSTEMI, all the patients were followed for one and six months to evaluate mid-term outcomes regarding mortality and major adverse cardiac events (MACE), defined as the occurrence of at least one of the events of myocardial infarction, repeated revascularization, or re-hospitalization.

Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by frequency (%) for categorical variables. Continuous variables were compared using t-test or non-parametric Mann-Whitney U test, whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the two study groups. Categorical variables were, on the other hand, compared using chi-squared test or Fisher's exact test when more than 20% of cells with expected count of less than five were observed. Cox proportional hazard model was used to determine main correlates of MACE. Statistical analysis was performed by SPSS version 21.0 (SPSS Inc., Chicago, IL). P values of 0.05 or less were considered statistically significant.

RESULTS

Totally, 124 patients were included in the study. The mean age of patients was 62.40 ± 11.07, ranging 35 to 93 years. Baseline demographic and clinical characteristics of patients are shown in Table 1.

Table1: Baseline Demographical and Clinical Characteristics in Patients with Non-ST Elevation Myocardial Infarction

Variables	Amount
Demographics	
Age (y)	62.4 ± 11.7
BMI (k/m^2)	26.28 ± 2.95
Male sex (%)	72.9
Medical History (%)	
Hypertension	56.5
Diabetes mellitus	33.9
Hyperlipidemia	50.8
Obesity (BMI > 30 kg/m^2)	29.8
Current smoking	34.9
Prior CABG	15.3
Prior PCI	12.1
Peripheral arterial disease	11.3
Prior heart failure	27.4
Prior cerebrovascular events	8.1
Prior renal failure	12.1
Chronic lung disease	15.3
Previous Aspirin use	52.4
Recent Function Class	
I	38.7
II	44.4
III	16.1
IV	0.8
Presentation Features	
Typical chest pain (%)	65.3
Chest pain + Dyspnea (%)	33.1
Atypical chest pain (%)	1.6
Initial heart rate (beats/min)	85.02 ±1.49
Initial systolic BP (mm Hg)	130.85 ± 26.22
ECG Findings (%)	
Pathologic Q wave	7.0
ST depression	68.5
Transient ST elevation	4.0
Laboratory Results	
Peak Troponin (µg/l)	3.08 ± 2.48
Peak CPK (IU/L)	631 ± 5.00
Peak CK.MB (IU/L)	87.06 ± 6.83
Hemoglobin (g/dL)	14.07 ± 1.68
Serum creatinine (mg/dL)	1.25 ± 0.32
TIMI Risk Score (%)	
Low risk (score 0-2)	6.5
Intermediate risk (score 3-4)	56.5
High risk (5-7)	37.1

Values are presented as percentages or mean± SD.

BP: Blood pressure; BMI: Body mass index; CABG: Coronary artery bypass grafting; ECG: Electrocardiogram; TIMI: Thrombolysis in Myocardial Infarction; PCI: Percutaneous coronary intervention.

The most common traditional cardiovascular risk factors were hypertension (56.5%), followed by hyperlipidemia, current smoking, diabetes mellitus, and obesity. Nearly one third of patient (27.8%) had history of coronary revascularization, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); about half had history of previous aspirin administration. Medical treatments during hospitalization, echocardiography and angiography findings are demonstrated in Table 2. Only a few patients (0.8%) received low molecular weight heparin instead of unfractionated heparin.

Approximately 96% of the patients underwent cardiac catheterization (37.1% within 24 hours from index admission and 58.1% after 24 hours), whereas 62.2% experienced percutaneous coronary intervention, 15.3% endured bypass surgery, and 22.5% were treated conservatively.

Based on the angiography report, three coronary vessel involvements were the most frequent results, followed by two vessel diseases (VD), one VD and left main disease (Table 2).

Regarding the one-month outcomes, one-month death occurred in 3.2%, re-hospitalization in 4.0%, CABG in 0.8%, and myocardial infarction in none of the patients. In addition, regarding the six-month outcomes, mortality rate was determined in 6.4%, re-hospitalization in 22.6%, CABG in 3.2%, and myocardial infarction in 4.8% of patients. Hence, one- and six-month MACE rates were 7.3% and 27.4%, respectively; survival rates at one and six months were 96.8% and 93.6%, respectively.

According to univariate analysis, different variants predict six-month MACE (Table 3); however, based on the Cox-proportion hazard modeling, only reduced left ventricular ejection fraction (LVEF) (HR = 0.909, P = 0.017), history of chronic kidney injury (HR = 8.884, P = 0.005), and Inotrope usage (HR = 35.759, P = 0.012) could predict six-month MACE.

In this context, none of the indexes including general coronary risk factors, echocardiography parameters, and level of cardiac enzymes could predict mortality rate.

DISCUSSION

According to the increasing trend of the overall incidence of NSTEMI compared with other components of acute coronary syndrome, the assessment of this ischemic event and also determining its related determinants are necessary. Besides, designing a risk stratification system to determine the level of risk in patients with NSTEMI can lead to better clinical management of these patients and also to schedule appropriate treatment programs for these patients.

In the present study, we first attempted to determine mid-term outcomes of patients with NSTEMI and then aimed to assess main predictors of NSTEMI outcomes in the study population. Based on observation, the mean age of patients NSTEMI was 62.40 ± 11.07 years, consistent with those of Korea Acute Myocardial Infarction Registry (KAMIR) (63.6 ± 12.2 years) [19]; but, they were younger than patients with NSTEMI in Malopolska Registry of Acute Coronary Syndromes performed by Dziewierz et al. (70.2 ± 11.6 years) [20]. The most frequent cardiovascular risk factor was hypertension, consistent with most NSTEMI studies [19-21]; however, smoking and hyperlipidemia were more common in a cohort study [22].

In this study, the mid-term mortality rate in patients with NSTEMI was 6.4%. Furthermore, one- and six-month MACE rates were 7.3% and 27.4%, respectively. On the other hand, although patients with NSTEMI had an acceptable mortality rate, they experienced a high mid-term MACE rate; among every four patients, one faced with cardiac morbidities in a mid-term period.

In one report, 458 patients without persistent ST segment elevation acute coronary syndrome were assigned to early invasive strategy. Hospital and overall mortality rates were 3.3% and 4.8%; respectively. MACE was observed in 20.3% of patients within six months [23].

Moreover, for the patient who had been referred for catheterization and the ones who underwent conservative strategy, Khalill et al. reported one-year mortality rate of 4% and 10%; respectively [24]. In another study performed by Park HW et al., the MACE rates for early term (one month) and late-term (one year) were 6.9% and 8.0%; respectively [25].

Table 2: In Hospital Medication, Echocardiography and Angiography Findings in Patients with Non-ST Elevation Myocardial Infarction

Variables	Amounts
Hospital Medication (%)	
UFH	99.2
LMWH	0.8
Aspirin + clopidegrol	67.7
Aspirin + clopidegrol + eptifibatide	32.3
Inotrope	5.6
Statin	100
Beta blockers	89.5
Calcium blockers	2.4
Echocardiography Parameters	
LVEF (%)	43.61 ± 11.35
LVEDD (cm)	5.34 ± 0.64
RVEDD (cm)	3.05 ± 0.28
Ea/Ee	12.44 ± 4.40
TAPSE (cm)	1.89 ± 0.27
MR (%)	
Mild	39.5
Moderate	19.4
Severe	2.4
Angiography Results (%)	
SVD	12.9
2VD	29.8
3VD	33.9
LMD	6.5

Values are presented as percentages or mean ± SD.
LMD: Left main disease; LMWH: Low-molecular-weight heparin; LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end diastolic diameter; MR: Mitral regurgitation; RVEDD: Right ventricular end diastolic diameter; SVD: Single vessel disease; 2VD: Two vessel disease; 3VD: Three vessel disease; TAPSE: Tricuspid annular plane systolic excursion; UFH: Unfractionated heparin.

Table 3: Comparison of Patients with NSTEMI according to 6-months MACE

Characteristics	MACE (+), (n = 34)	MACE (-), (n = 90)	P value
Male gender	27 (79.4)	63 (70)	0.295
Age (y)	66.41 ± 10.64	60.88 ± 10.90	0.013
BMI (kg/m2)	25.56 ± 2.31	26.55 ± 3.13	0.097
Hypertension	23 (67.6)	43 (47.8)	0.122
Diabetes mellitus	12 (35.3)	30 (33.3)	0.837
Current Smoking	16 (47.1)	27 (30.0)	0.032
Hyperlipidemia	16 (47.1)	47 (52.2)	0.608
Prior CABG	9 (26.5)	17 (18.9)	0.019
Prior PCI	4 (11.8)	11 (12.2)	0.889
Prior heart failure	19 (55.9)	15 (16.0)	< 0.001
Prior renal failure	9 (26.5)	6 (6.7)	0.003
Prior cerebrovascular events	3 (8.8)	7 (7.8)	0.849
Peripheral arterial disease	6 (17.6)	8 (8.9)	0.169
Opium	7 (20.6)	7 (7.8)	0.132
LVEF	34.44 ± 13.30	47.08 ± 8.61	< 0.001
LVEDD	5.77 ± 0.78	5.18 ± 0.49	< 0.001
RVEDD	3.12 ± 0.31	3.03 ± 0.26	0.066
TAPSE	1.7 ± 0.3	1.93 ± 0.2	0.005
Ea/Ee	13.7 ± 4.7	11.9 ± 4.3	0.060
MR			
Mild	12 (35.3)	37 (41.1)	0.149
Moderate	14 (41.2)	10 (11.1)	0.001
Severe	1 (2.9)	2 (2.2)	0.889
TIMI Score	4.7 ± 1.2	3.9 ± 1.2	0.001
ACC/AHA high risk	21 (63.6)	26 (28.5)	0.001
ACC/AHA moderate risk	11 (33.3)	58 (63.7)	0.004
ACC/AHA low risk	1 (3.0)	7 (7.6)	0.32
Previous Aspirin usage	20 (60)	45 (49)	0.185
Drugs in hospitalization			
Aspirin + Clopidegrol	27 (79.4)	57 (63.3)	0.251
Aspirin + Clopidegrol + Eptifibatide	7 (20.6)	33 (36.7)	0.095
UFH	34 (100)	89 (98.9)	0.537
Inotrope	6 (17.6)	1 (1.1)	0.002
Beta blockers	24 (70.6)	87 (96.7)	0.226
Pathologic Q wave	4 (11.8)	0	0.005
ST-T change	27 (79.4)	58 (64.4)	0.001
Angiography within 24h	7 (21.2)	39 (43.3)	0.035
Angiography results			
SVD	1 (3.1)	15 (17.2)	0.005
2VD	7 (20.6)	30 (34.5)	0.021
3VD	15 (46.9)	27 (31.0)	0.001
LMD	3 (9.4)	5 (5.7)	0.445

Values are presented as n (%) or mean ± SD.
Abbreviations are as in Tables 1 and 2. MACE: Major adverse cardiac events.

From the CRUSADE registry, one-year mortality rate in older patients with NSTEMI (aged ≥ 65 years) was 24.4%, and age was the most significant predictor of mortality [21]. Recently, Kim et al. reported a six-months MACE ranging from 12.4% to 23.1% based on TIMI risk score for low- to high-risk patients with NSTEMI, respectively, in KAMIR [19].

In the second step of study, we found that patients with MACE were older and more likely to be current smokers, have a history of CHF, CABG, CKD, pathologic Q wave, ST-segment changes, LV and RV dysfunction, moderate MR, catheterization after 24 hours, and inotrope usage during hospitalization; however, the correlation of severe MR and MACE was not statistically significant, which may be due to insufficient total number of severe MRs. The TIMI risk score (TRS) system

had a good correlation with MACE for patients in the high-risk group. By Cox-proportion hazard analysis, we could introduce reduced LVEF, history of chronic kidney injury, and Inotrope use as major factors triggering mid-term MACE in patients with NSTEMI.

In KAMIR by Kim et al., Killip class above III, the presence of heart failure or cardiogenic shock and NT-ProBNP demonstrated good correlations with MACE, and the TRS system had a good correlation with MACE for patients in the low and intermediate groups [19].

On the other hand, demographic parameters, echocardiography indexes and also increased level of cardiac enzymes were not correlated with poor mid-term outcome in those patients.

It seems that the type of predictors of NSTEMI consequences can be different in various populations depending on characteristics of population, diagnostic criteria of MACE, follow-up time, and number of patients included.

This study revealed that in a limited portion of the Iranian population, only three factors including reduced LVEF, history of chronic kidney injury, and Inotrope usage could predict six-month MACE, suggesting that the abovementioned parameters are probably more significant than other prognostic factors reported.

Limitations of this study can be discussed from various points. First, a small number of participants was used; thus, the findings should be treated with care. Second, other variables could provide novel prognostic results. Third, further studies need to be accomplished to achieve verification of new scoring systems.

In conclusion, patients with NSTEMI may face high six-month MACE, which can be predicted by low LVEF, history of renal injury, and use of inotrope.

Therefore, defining a risk stratification system should be considered in these patients.

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CONFLICTS OF INTEREST

There is no conflict of interest for the present study.

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Association of Anticardiolipin Antibodies and Extent of Coronary Artery Disease in Military Personnel and Non Military Population With Acute Coronary Syndrome

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Abstract

Introduction: Cardiac involvement is one of the chief complications considerably contributing to the morbidity and mortality of patients with systemic autoimmune diseases. Anticardiolipin antibody is a marker of elevated myocardial infarction risk and it also predicts post cardiac intervention risk. In the current study, we aimed to evaluate the association between anticardiolipin IgM and IgG levels and atherosclerotic involvement of coronary arteries.

Methods: Patients with acute coronary syndrome admitted to a military hospital were included in the study. Patients were categorized to military personnel and non-military personnel. Laboratory data including lipid profile, blood sugar, anticardiolipin IgM and anticardiolipin IgG were verified. Existence and the extent of Coronary Artery Disease (CAD) were defined according to angiographic findings. The relationship between anticardiolipin antibody levels and the number of vessels were evaluated.

Results: According to our sample population calculation, we performed the study on a total of 92 patients. Measurement of both anticardiolipin antibodies (IgM and IgG) in military personnel and non personnel patients showed no significant difference. In both military personnel and non personnel groups, there was a significant association between anticardiolipin IgM and IgG levels and number of coronary arteries with significant stenosis. The C Reactive Protein (CRP) level was significantly higher in military personnel.

Conclusions: According to the study results, anticardiolipin antibody levels were the same in both military personnel and non personnel. Also systolic and diastolic blood pressures were not significantly different in both groups. Increased CRP level in military personnel may be a warning signal about the possibility of premature CAD in this population, hence aggressive risk factor modification is recommended. Paradoxically lipid profile and FBS levels were more favorable in military personnel, which indirectly reflects their higher state of physical activity.

INTRODUCTION

Atherosclerosis is a multifactorial process, which initiates in early life but presents clinically later in life. Atherosclerosis is progressively more considered an immune-mediated process. Epidemiological studies revealed an increase of cardiovascular events in patients affected by systemic autoimmune diseases. All the anatomical heart structures can be affected, and several pathogenic mechanisms have been reported [1]. Antiphospholipid Syndrome (APS) is a disorder that manifests clinically as recurrent venous or arterial thrombosis and/or fetal loss. Antiphospholipid (APL) antibodies are a group of antibodies directed against epitopes on plasma proteins that are uncovered by binding of these proteins to anionic phospholipids on plasma membranes. Characteristic laboratory abnormalities in APS, include persistently elevated levels of antibodies directed against membrane anionic phospholipids (i.e. Anticardiolipin [ACL] antibody,

antiphosphatidylserine) or their associated plasma proteins, predominantly beta-2 glycoprotein I (apolipoprotein H), or evidence of a circulating anticoagulant [2-5].
Anticardiolipin antibody is a member of autoantibodies, which directly acts against protein- phospholipid complex. Elevated levels of these antibodies are associated with a clinical syndrome in which venous and arterial thrombosis occurs [6-9]. In addition to antiphospholipid antibody syndrome, anticardiolipin level elevates in a variety of autoimmune diseases especially in SLE [10]. A subset of people with no apparent autoimmune disease, have elevated anticardiolipin levels.
Early findings about the clinical importance of anticardiolipin antibodies came from SLE patients [11]. In SLE, patients with higher titers of anticardiolipin antibody had more vascular events including arterial thrombosis [12]. Interestingly, 14% of patients with thrombotic brain ischemia had marked elevation of anticardiolipin antibody [13, 14]. Anticardiolipin antibody is a marker of elevated myocardial infarction risk and it also predicts post cardiac intervention risk [15].
These observations support the possible role of autoimmunity in the genesis of atherosclerosis that may have clinical or subclinical features. The clinical edge of this phenomenon is Coronary Artery Diseases (CAD), while early endothelial dysfunction, abnormalities of circulation or atherosclerotic plaques, detected by different imaging techniques, identifies the subclinical atherosclerosis expression. According to different reports, traditional risk factors were not different in APS and in the general population [16]. In agreement with these findings, APS patients have an increased rate of cardiovascular incidents: myocardial infarction appears at same stage of the disease in up to 5.5% and is the presenting manifestation in 2.8% of APS patients [17].
In spite of the mentioned studies, some researchers have shown that there is no robust association between anticardiolipin levels and cardiovascular risk. In addition, evidence for the relationship between anticardiolipin antibody and atherosclerosis is limited.In the current study, we aimed to evaluate the association between anticardiolipin IgM and IgG levels and atherosclerotic involvement of coronary arteries with an angiographic study.

METHODS

This study had a cross sectional design in order to evaluate the relationship between anticardiolipin level and the extent of coronary artery disease. Patients with acute coronary syndrome admitted to 502 military hospitals of the Islamic Republic of Iran were included in the study. Patients were categorized to two groups. The first group comprised of military personnel, who were admitted with Acute Coronary Syndrome (ACS) diagnosis and underwent coronary angiography to delineate the coronary anatomy, this group was defined as our case group. The second group composed of non military patients, who were admitted to the 502 military hospitals with the diagnosis of ACS and underwent coronary angiography, this group was defined as the control group. All patients with ACS and the high risk criteria became candidates of coronary angiography, according to our current standard guidelines. Exclusion criteria included any active or chronic inflammatory disease, acute or chronic infectious disease, known autoimmune disease and consumption of certain drugs including phenothiazin, hydralazine, procainamide and prednisone within the past year. To determine the sample population we relied on data obtained by the study of Eber et al [18].
Demographic, clinical and paraclinical data were gathered in a questionnaire, according to the medical records of the patients. Clinical variables including systolic and diastolic blood pressures were recorded. Laboratory data including lipid profile, blood sugar, anticardiolipin IgM and anticardiolipin IgG were verified. Existence and the extent of CAD was defined according to the angiographic findings. Significant CAD was defined as the existence of more than 50% diameter luminal stenosis of the coronary arteries. Once concent was provided by the patients, 5 cc of blood was drained extra to the routine blood sampling to measure the anticardiolipin level with the Enzyme Linked Immunosorbent Assay (ELISA). The study protocol was approved by the medical ethics committee of the Islamic Republic of Iran military force and all procedures were designed according to the declaration of Helsinki. After providing detailed oral information to participants, written informed consent was obtained from each participant. The study was intended to be triple blind. Patients, laboratory technicians, physicians in charge of angiography and the statistics specialist were all unaware of the aims of study and about the importance of comparison between military personnel and non personnel patients.
To assess variables, quantitative results were declared in the form of mean +/- standard deviation and qualitative variables were stated with their percentages. In order to evaluate the relationship between the anticardiolipin antibody levels (IgM and IgG) and the number of vessels with significant stenosis in angiography, we used One-way Analysis of Variance (ANOVA) statistical test.
In order to document the association between employment in the military service and anticardiolipin antibody level and number of involved coronary arteries, we used the Cumulative Logit Modeling statistical test. To analyze the results, the SPSS software version 9.1 and SAS software version 16 were used. For stating the statistical significance, p values of level less than 0.05 were considered statistically meaningful.

RESULTS

According to our sample population calculation, we performed the study on a total of 92 patients (46 patients in military personnel group and 46 patients in the nonmilitary personnel group). All patients in the military personnel group were male while only 58.7% of participants in the non military group were male. Patients in the military personnel group were significantly younger than the patients in the non-military personnel group. There was no significant difference in systolic blood pressure in the two groups (Table 1).
In the laboratory findings, C Reactive Protein (CRP) level was significantly higher in the military personnel group than the non-military personnel. In contrast, military personnel had significantly lower total cholesterol and Fasting Blood Sugar (FBS) levels and higher high density cholesterol level (Table 1). Furthermore, 60.9% of military personnel and 80.3% of non military personnel had no significant stenosis of coronary arteries in angiography. Distribution of involved vessels and the frequency of left main disease were the same in the two groups but the percentage of three vessel disease was higher in the military personnel than the non personnel (19.6% versus 10.9%) (Table 2).

Table 1 Demography and Baseline Laboratory Finding of the Patients

Features	Military Personnel	Non Personnel	P value
Male	46 (100)	27(58.7)	< 0.001
Age (years)	49.6 ± 5.6	54.4 ± 11.1	0.01
Systolic blood pressure (mmHg)	132.2 ± 17.2	126.0 ± 17.8	0.127
Positive CRP	12 (21.7)	1(2.2)	0.004
ESR (mm/h)	14.3 ± 9.1	16.9 ± 14	0.327
FBS (mg/dL)	102.7 ± 23.4	139.4 ± 20.5	< 0.001
Total cholesterol (mg/dL)	234.9 ± 59.2	265.9 ± 42.5	0.006
Triglyceride (mg/dL)	158.3 ± 35.6	161.5 ± 79.8	0.810
LDL (mg/dL)	119.6 ± 29.3	129.7 ± 39.4	0.187
HDL (mg/dL)	38.5 ± 10.4	32.7 ± 2.5	< 0.001

CRP: C reactive protein; ESR: erythrocyte sedimentation rate; FBS: fasting blood sugar; HDL: high density cholesterol; LDL: low density cholesterol
Data are presented as No (%) or mean ± SD

Table 2: Angiography Features of the Patients

	Military Personnel	Non Personnel	P value
Distribution of CAD			
LAD	18 (39.1)	18 (39.1)	0.999
LCX	9 (19.6)	11 (23.9)	0.613
RCA	9 (19.6)	11 (23.9)	0.613
Number of vessels with significant stenosis			
Normal	28 (60.9)	25 (84.3)	> 0.05
1 vessel disease	9 (19.6)	7 (15.2)	> 0.05
2 vessel disease	0 (0)	9 (19.6)	> 0.05
3 vessel disease	9 (19.6)	5 (10.9)	0.014
Left main stenosis	0 (0)	1 (2.2)	0.999

LAD: left anterior desending artery; LCX: left circumflex artery; RCA: right coronary artery Data are presented as No (%)

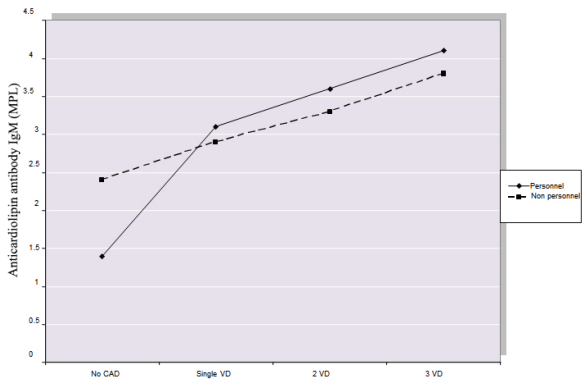

Figure 1: Association of Anticardiolipin Antibody IgM and Number of Coronary Stenosis

Measurement of both anticardiolipin antibodies (IgM and IgG) in military personnel and non personnel patients showed no significant difference. Consequently, employment in the military service does not alter the level of anticardiolipin antibodies. Anticardiolipin IgM antibody level in military personnel and military non personnel patients were 1.973.04 ± MPL units and 1.94 ± 2.66 MPL units, respectively. Anticardiolipin IgG antibody level in military personnel and military non personnel were 2.55 ± 4.14 GPL units and 2.71 ± 3.88 GPL units, respectively. In both military personnel and non personnel groups, there was a significant association between anticardiolipin IgM levels and number of coronary arteries with significant stenosis (Fig 1).

Anticardiolipin antibody IgM level in patients with normal coronary arteries in military personnel and non military personnel were 1.4 and 2.4 MPL units, respectively. The IgM antibody level with single vessel coronary artery disease in military personnel and non military personnel were 3.1 and 2.9 MPL units, respectively. In patients with two vessel coronary artery disease, IgM antibody level in military personnel and military non personnel patients were respectively 3.6 and 3.3 MPL units. Finally three vessel coronary artery involvement in military personnel and non personnel groups had IgM antibody level of 4.1 and 3.8 MPL units, respectively ($P < 0.05$). In addition, in both military personnel and non personnel groups, there was a significant association between

anticardiolipin IgG levels and number of coronary arteries with significant stenosis (Table 3).

Table 3: Anticardiolipin IgG Antibody Level in Patients Who Underwent Angiography

IgG level (GPL)	Military Personnel	Non Personnel	P value
Normal Coronary arteries	1.5 ± 0.1	3.2 ± 0.2	< 0.05
1 vessel disease	3 ± 0.2	3.6 ± 0.3	< 0.05
2 vessel disease	4.1 ± 0.5	3.9 ± 0.3	< 0.05
3 vessel disease	5.4 ± 0.3	4.9 ± 0.5	< 0.05

Data are presented as mean±SD

DISCUSSION

Some novel risk factors that could contribute to atherosclerosis development have been reported recently. These include inflammatory markers, including CRP, fibrinogen, interleukin-6, CD40/CD40L, adhesion molecules, and immunological factors including anticardiolipin (ACL), anti-β2GPI, anti-oxLDL and anti-HSP antibodies. Several autoantibodies are associated with atherosclerosis and its manifestations in humans [19].

Antiphospholipid Syndrome is a prothrombotic state characterized by recurrent arterial and venous thrombosis, recurrent pregnancy loss, and the presence of circulating antiphospholipid antibodies. Thrombophilia may be associated with premature atherosclerosis, and accelerated atherosclerosis was suggested as an additional clinical feature of APS. This pathological process may be mediated by direct proinflammatory and procoagulant activity that APLs exert on endothelial cells or indirectly, via the inflammatory/immune mechanisms that have been implicated in autoantibody-mediated thrombosis [20]. Veres et al. showed a correlation between serum levels of ACL and anti-β2GPI antibodies and the incidence and severity of acute coronary syndrome, MI and stroke [21]. Therefore, non-traditional risk factors such as antibodies seem to be involved in APS-associated atherogenesis. In vitro, APL accelerates the process of plaques formation, enhancing the macrophages transformation to foam cells by oxLDL [22].

The actual frequency of APS in the general population is unknown. One to 5% of healthy individuals have APL antibodies. Furthermore, ACL antibodies tend to be found more frequently in elderly persons; thus, positive titer results should be interpreted with caution in this population. The APL antibodies are found in approximately 30-40% of patients with SLE, but only about 10% have APS [23].

Antiphospholipid Syndrome is more common in young to middle-aged adults; however, it also manifests in children and elderly people. A female predominance has been documented, particularly for secondary APS. This parallels the association of APS with SLE and other connective-tissue diseases, which also have a female predominance [24]. Patients with APS are prone to cardiovascular events. Coronary artery events and valvular heart disease are common features of this syndrome [25]. Consequently, early diagnosis, aggressive risk factor modification and proper management may reduce the cardiovascular burden in patients with APS. In this study, in addition to the measurement of anticardiolipin antibody levels and evaluation of their relationship with number of coronary artery stenosis, we further explored the differences in military and nonmilitary personnel.

According to the study results, anticardiolipin antibody levels were the same in both military personnel and non personnel patients. Also systolic and diastolic blood pressures were not significantly different in both groups. As mentioned in the result section, CRP level was higher in the military personnel group. Chronic inflammation is pivotal in heart disease; studies have shown that high levels of CRP, measured by high-sensitivity CRP (hs-CRP), can be a marker of atherosclerosis. High sensitivity-CRP is an important predictor for cardiovascular events, including myocardial infarction, cerebrovascular events, peripheral vascular disease and sudden cardiac death in individuals without a history of heart disease. In patients with acute coronary disease, CRP level predicts mortality and cardiac complications [26]. High CRP levels portend a worse prognosis in patients with acute coronary syndromes. High sensitivity-CRP is also a marker of metabolic syndrome [27].

Increased CRP level in military personnel may be a warning signal about the possibility of premature CAD in this population, hence aggressive risk factor modification is recommended. Paradoxically, lipid profile and FBS levels were more favorable in military personnel group, which indirectly reflects their higher state of physical activity. In angiography, as stated although military personnel had higher frequency of coronary artery disease, the difference was not statistically significant. The subgroup of patients with three-vessel CAD had significantly higher frequency in military personnel. Considering the higher CRP level in military personnel, and the predictive value of CRP, aggressive modification of CRP and inflammatory state in all patients and particularly in military personnel seems reasonable [28-31].

According to the findings of the current article, anticardiolipin antibody levels are not different in military and non military personnel but in both groups the higher titers of antibodies are associated with more extensive CAD. In conclusion, in this study we showed the importance and association of anticardiolipin antibodies and CRP with the extent of CAD. Further research is recommended for exploring these issues to target the atherosclerosis process more efficiently.

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The Effect of Hyperuricemia on the Rate of Contrast-Induced Nephropathy in Patients with Coronary Angiography

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Abstract

Introduction: There is little information about the relationship between hyperuricemia and contrast induced nephropathy. The present study aimed to evaluate the relationship between hyperuricemia and contrast induced nephropathy among patients, who had undergone coronary angiography.

Methods: In the current study, 200 consecutive patients with coronary artery disease, who underwent coronary angiography in Modarres hospital, were enrolled. According to the available data, the upper limit normal level of uric acid was defined as 7 mg/dl in males and 6.5 mg/dl in females. By increasing level of serum creatinine to 0.5 mg/dl (or 25% enhancement) from basic level of creatinine during 48 hours of introduction of contrast agent, diagnosis of Contrast Induced Nephropathy (CIN) was established. The relationship between hyperuricemia and CIN was then assessed.

Results: There is a significant difference between normouricemic patients and hyperuricemic patients, in aspect of weight ($P = 0.011$) and uric acid ($P = 0.001$); however, other quantitative and qualitative variables including age, volume of contract agent, creatinine level after angiography, hemoglobin level, gender, arterial access type, number of involved vessels, were insignificant between the two groups ($P > 0.05$). Moreover, as an essential finding, CIN was shown in 9% of normouricemic patients and 10% of hyperuricemic patients with no significant difference between the two groups ($P = 0.6$).

Conclusions: Our study suggests that hyperuricemia may not significantly increase the rate of the contrast-induced nephropathy in patients, who had undergone angiography.

INTRODUCTION

Contrast-Induced Nephropathy (CIN) is defined as acute reduction kidney function, according to 25% or 0.5mg/dl increase in serum creatinine during 48 hours since introduction of contract agent [1, 2]. It is the third cause of acute renal failure and such patients have high rates of vascular complications and longer hospitalization time [3-6]. Renal failure following CIN may lead to hemodialysis for the involved patients that leads to escalating hospital mortality up to 40% and mortality during the next two years up to 80%. Hyperuricemia, as a risk factor, plays an important role in various types of diseases. Nevertheless, there is little information about the relationship between hyperuricemia and CIN; for instance, by tubular obstruction, uric acid plays its role in pathogenesis of CIN. Moreover, through increasing oxygen radicals, activation of Renin–Angiotensin System (RAS), rising level of Endothelin 1 and inhibition of nitric oxide, hyperuricemia is involved in pathogenesis of CIN [7-12]. According to increasing rate of coronary angiography and angioplasty, and considering the fact that CIN is a relatively common and preventable condition, the present study evaluated the relationship between hyperuricemia and contrast induced nephropathy among patients, who had undergone coronary angiography.

METHODS

In the current study, 100 consecutive patients with hyperuricemia and 100 consecutive normouricemic patients with coronary artery disease, who had undergone coronary angiography at Modarres hospital, during 2013 to 2014, were enrolled. According to the available data, the upper limit normal level of uric acid was defined as 7 mg/dl in males and 6.5 mg/dl in females. The exclusion criteria of this study were being

pregnant, receiving contract agent during the last week and having Glomerular Filtration Rate level (GFR) less than 30. Increasing level of serum creatinine to 0.5 mg/dl (or 25% enhancement) from basic level of creatinine during 48 hours of introduction of contrast agent was defined as CIN. The relationship between hyperuricemia and CIN was assessed. Descriptive and analytic studies were performed using the SPSS (version 21) software; in order to describe the data, average and frequency percentages were used, and Chi square and Independent T-test were used for analysis of qualitative and quantitative data, respectively. P-values of less than 0.05 were considered statically significant. A written informed consent was obtained from all participants and the institutional review board approved the study.

RESULTS

The total number of 200 patients enrolled in our study was divided to two groups including: 100 normouricemic patients and 100 hyperuricemic patients. In order to compare quantitative variables of this study, both groups of patients were analyzed by independent T-test. Based on this test, there was a significant difference between normouricemic patients and hyperuricemic patients, in aspects of weight (P = 0.011) and uric acid (P = 0.001); however, other quantitative variables including age, volume of contract agent, creatinine level before and after angiography and hemoglobin level had no significant differences (P > 0.05). In order to compare the qualitative variables of both groups of patients (normouricemic patients and hyperuricemic patients), Chi Square test was performed. On this basis, the relationship of qualitative variables including gender, arterial access type, number of involved vessels, and left ventricular ejection fraction was insignificant between the two groups (P > 0.05).

Moreover, as an important finding, contrast-induced nephropathy was shown in 9% of normouricemic patients and 10% of hyperuricemic patients that showed no significant difference between the two groups (P = 0.6).

DISCUSSION

In our study, which was performed to determine the relationship between hyperuricemia and CIN, according to the aforementioned definition, in normouricemic patients 9% and in hyperuricemic patients 10% had CIN. The research of Omer Toprak et al. on 266 patients, who underwent angiography for determining the frequency of CIN among 126 hyperuricemic patients and 120 normouricemic patients, showed that the incidence of CIN in normouricemic and hyperuricemic patients was 2.9% and 15.1%, respectively [13, 14]. In fact, comparing results of the study of Omer Toprak et al. with the present study revealed that amongst both groups of normouricemic and hyperuricemic patients, other factors had interference in occurrence of CIN. Comparing results of the present research with the research of Yong Liu et al. on patients that had undergone angiography for determining the frequency of CIN among 211 hyperuricemic patients and 577 normouricemic patients showed that the incidence of CIN in normouricemic and hyperuricemic patients was 1.4 and 8.1%, respectively. Results of the study by Yong Liu et al. demonstrated that among both groups of normouricemic and hyperuricemic patients, other factors including age older

Table 1: Comparison between of Normouricemia and Hyperuricemia Group

	Normouricemia Group (N = 100)	Hyperuricemia Group (N = 100)	P value
Age	58.93 + 10.76	61.23 + 10.43	NS
Sex (male)	69 (69%)	60	NS
weight (kg)	73.700 ± 12.23	78.380 ± 13.47	0.011
Hypertension	56	63	NS
Diabetes mellitus	30	28	NS
Hyperlipidemia	42	41	NS
Smoker	33	37	NS
creatinine level before angiography (mg/dl)	1.15 ± 0.23	1.15 ± 0.22	NS
creatinine level after angiography (mg/dl)	1.20 ± 0.43	1.41 ± 0.59	NS
Hemoglobin level (mg/dl)	13.42 ± 1.76	13.67 ± 1.81	NS
Uric acid (mg/dl)	4.90 ± 1.24	7.84 ± 1.35	0.001
Redial arterial access	15	15	NS
number of involved vessel			NS
1VD	68	78	
2VD	27	16	
3VD	4	6	
EF			NS
EF>50	30	35	
30>EF>50	60	50	
30<EF	10	15	
Volume of contract agent	338.30 ± 142.25	306.20 ± 139.65	NS
Contrast induced nephropathy	9%	10%	NS

EF: Left ventricular ejection fraction,
Data are presented as mean ± SD, No (%) and No.

On the other hand, according to the study of Maryam Pakfetrat et al., CIN occurred in 15.5% of patients and revealed that level of serum creatinine before angiography, volume of contrast agent, diabetes mellitus and dehydration had a significant relationship with occurrence of CIN; nevertheless, age, gender and level of uric acid had no significant difference among the two groups including CIN group and non CIN group [16]. The results of these studies and our study suggested that there are some controversies about factors that increase the level of serum creatinine after angiography, which may be due to different conditions and interfering factors of various studies.

Our study suggests that hyperuricemia may not significantly increase the rate of the contrast-induced nephropathy in patients, who had undergone angiography. Studies with large sample sizes and detailed categorization were recommended for future investigations.

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Int J Cardiovasc Pract. **Original Article**

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Chronic Total Occlusion-Angioplasty with Antegrade Approach: A two-Year Experience in "Modarres Hospital", A Tertiary University Hospital, Tehran, Iran

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Abstract

Introduction: New techniques for the percutaneous treatment of coronary chronic total occlusions (CTO) have had a high success rate since a few years ago, so the interest for this treatment has been increasing these days.

Methods: The current observational study was performed in Modarres hospital as a tertiary referral center. All the patients with documented stable angina who had failed to response to full guideline-mediated medical therapy, referred to our hospital, were candidates for coronary angiography. Antegrade strategy was applied for all these patients. The length of the lesion, the fluoroscopy time of the CTO angioplasty, consumed contrast volume, the number of guide wires used, whether a corsair or tornus micro-catheter was used or not, and the success rate of the angioplasty were documented for further analysis.

Results: A total of 47 patients with documented stable angina were finally included. The median age was 59 (45-78) and 70.2% were male. The mean length of the lesion was 34.0 ± 1.1 .The mean fluoroscopy time and contrast volume were 57.9 ± 3.2 minutes and 525.9 ± 20.9 mL, respectively. In average, 2.2 guide wires were used. Corsair and tornus micro-catheters were applied in 30 (63.8%) and 5 (10.6%) of the cases, respectively. Seven complications (all including coronary dissection) occurred. In-hospital major adverse cardiac events (MACE) rate was 10.6%, all of which were non-Q wave myocardial infarction. The success rate was 85.1%. The higher number of used wires, use of corsair, and tornus micro-catheter were not significantly concordant with success rate (P-value > 0.05); in addition, longer lesions was not concordant with unsuccessfulness rate (P-value > 0.05).

Conclusions: Patient selection for CTO-angioplasty should be performed more carefully. Patients' quality of life and risk of probable procedural complications and future cardiac events should be assessed to decide the best treatment approach. Radiation exposure, contrast consumption and fluoroscopy time are recommended to be monitored during the procedure and thresholds should be defined to enhance safety and efficacy.

INTRODUCTION

Coronary chronic total occlusions (CTOs) are described by substantial atherosclerotic plaque burden within the artery, due to complete obstruction of the vessel. While the period of occlusion is challenging to define on clinical fields, a total occlusion should be present for at least three months to be delineated a proper CTO [1]. The presence of a CTO is one of the most frequent aims for Coronary artery bypass grafting (CABG) referral. Percutaneous coronary intervention (PCI) of chronic total occlusions has traditionally been restricted by technical success rates of 50% to 70%, despite being accomplished in greatly selected cases [2, 3].

New techniques and devices increase the interest for the per-

cutaneous treatment of coronary CTOs with a higher success rate than a few years ago. Percutaneous treatment for these lesions improves the symptoms and prognosis of patients in the stable phase of coronary disease. Current advances in interventional guide wires, catheters, and innovative methods have resulted in noteworthy progresses in success ratios with percutaneous coronary intervention [4-6]. In the present observational study, we explain our experiences in CTO PCI in a single center of PCI and describe data in a two-year period.

METHODS

The current observational study was performed in Modarres hospital as a tertiary referral center from September 2013 to December 2015. All the patients with documented stable angina who had failed to response to full guideline-mediated medical therapy, referred to our hospital, were candidates for coronary angiography. In addition, every patient with any type of acute coronary syndrome was excluded from the study. Standard angiography was conducted in an elective state for patients with femoral approach and if the angiography revealed CTO lesion criteria in one vessel territory, those cases were considered as final included patients in the study. The Institutional Review Board approved the study protocol and patients provided informed written consents.

Antegrade strategy was applied for all the patients. Length of the lesion, fluoroscopy time of the CTO angioplasty, consumed contrast volume, the number of guide wires used, whether or not corsair or tornus micro-catheter was used, and the success rate of the angioplasty were documented for further analysis. SPSS statistical software version 20.0 for windows (SPSS Inc., Chicago, IL) was applied. Independent sample t-test was used for quantitative studies. P values less than 0.05 were considered statistically remarkable.

RESULTS

A total of 47 patients with documented chronic stable angina were finally included. The median age was 59 (45-78) and 70.2% of patients were male. All the lesions were type C with pre-procedure TIMI flow grade 0. The mean length of the lesion was 34.0 ± 1.1 .The mean fluoroscopy time and contrast volume were 57.9 ± 3.2 minutes and 525.9 ± 20.9 mL, respectively. In average, 2.2 (2-4) guide wires were used. Corsair and tornus micro-catheters were applied in 30 (63.8%) and 5 (10.6%) cases, respectively. Seven complications (all including coronary artery dissection) occurred. In-hospital major adverse cardiac events (MACE) rate was 10.6%, all of which were non-Q wave myocardial infarction. All the results are shown in Table 1. The success rate was 85.1%. Higher number of used wires, use of corsair, and tornus micro-catheter were not significantly concordant with success rate (P-value > 0.05); in addition, longer lesions was not concordant with unsuccessfulness rate (P-value > 0.05) (Table 1).

DISCUSSION

Improvement in symptoms, enhancement in left ventricular function, and increase in survival are the potential benefits of CTO PCI [3]. PCI for CTO is associated with a substantial use of laboratory catheterization supplies. Moreover, procedure and fluoroscopic times double, as time-consuming as those for PCI for non-CTO lesions; CTO PCI can also result in improvident use of laboratory catheterization supplies and interventionists time, which can reduce the patient flow through the laboratory [7]. Furthermore, the extent of equipment required for successful achievement of the process can be more than that of standard PCI, because interventionists will often need multiple guiding catheters, guide wires and other devices to execute the procedure [8].

The risk of radiation injury and contrast nephropathy potentially affect CTO-angioplasty. In our center, the mean fluoroscopy time of 57.9 ± 3.2 minutes and contrast volume of 525.9 ± 20.9 mL were relatively higher than the average CTO angioplasty in other centers, which should be considered in further procedures to be reduced [9, 10]. The rate of complications and in-hospital major cardiac events in our center were comparable with other centers' results [9, 11, 12]. Coronary dissection consisted of all the CTO-angioplasties in our center.

Table1: Results of CTO-angioplasty with Ante Grade Approach

Characteristics	N = 47
Mean age	59 (45-78)
Sex (male)	32 (70.2)
Mean fluoroscopy time (minutes)	57.9 ± 3.2
Mean contrast volume (ml)	525.9 ± 20.9
Sheath size	
7French	30 (63.8)
6French	17 (36.2)
Number of guide-wires used	2.2 (2- 4)
Use of Corsair micro catheter	30 (63.8)
Use of Tonus micro catheter	5 (10.6)
Left coronary guiding catheter	
Extra backup (XB)	44 (93.6)
Left Amplatz	2 (4.3)
Left Judkins	1 (2.1)
Right coronary guiding catheter	
Left Amplatz	46 (97.9)
Right Judkins	1 (2.1)
Success rate	40 (85.1)
In-hospital MACE*	5 (10.6)
Complications**	5 (10.6)

Values are presented as No (%), mean (range) and mean ± SD.
MACE: major adverse cardiac events
*All were non-Wave MI
**All were coronary artery dissection

Considerable scholar and economic resources have been provided in the effort to conquer the complexity in crossing CTOs with a wire. Special new designed wires and techniques have been explained. A range of devices have been demonstrated in an effort to overcome wire-crossing complexity [13-15]; however, as a vague result, use of corsair or tornus micro-catheter were not significantly concordant with success rate in our observational study; although, we should judge about this result with caution because of our relatively small sample size. While the antegrade strategy was applied

for all the patients in our study, the success rate was relatively prominent. CTO PCI is speedily developing into its own field of interventional cardiology. Improving success necessitates long-term promise to master the extensive variety of accessible techniques, each of which may offer the only way to success in distinct cases.

Our study was a single center study. As it is known, CTO angioplasty is less popular in comparison with CABG of these lesions, even regarding some escalation in trends to CTO-PCI in recent years. This study could be considered as a pilot study and a new window for future large and multicenter studies, which will reveal more detailed results. Moreover, valuable clinical and systematic reviews could be published from results of various centers. It is recommended for future large sample-size studies to have long duration follow-ups.

Treatment of CTO lesions has developed in recent years as a consequence of a rebellion in medical equipment, which facilitates these patients to be treated with success rates higher than a few years ago. However, patient selection for CTO-angioplasty should be performed more carefully. Patients' quality of life and risk of probable procedural complications and future cardiac events should be assessed to decide the best treatment approach. Radiation exposure, contrast consumption and fluoroscopy time are recommended to be monitored during the procedure and thresholds should be defined to enhance safety and efficacy.

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Int J Cardiovasc Pract. **Case Report**

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Cardiac Failure Secondary to Hypocalcemia

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Abstract

Hypocalcemic cardiomyopathy due to hypoparathyroidism is a very atypical and rare circumstance, which is usually intractable to conventional therapy for cardiac failure, but responds satisfactorily to restoration of normocalcemia.

We describe a young woman who developed clinical signs of hypocalcemia due to hypoparathyroidism, reduced left ventricular ejection fraction and polymorphic ventricular tachycardia as consequences of hypocalcemia.

This case underscores the importance of biochemical abnormalities like hypocalcemia as a rare cause of secondary cardiomyopathy and emphasizes on the need for effective and immediate treatment of hypocalcemia and its related causes.

INTRODUCTION

Dilated cardiomyopathy could be primary or secondary. Even if some causes are familiar, such as toxic agents (alcohol or drugs of chemotherapy) or viral and bacterial infections, biochemical abnormalities are much less common [1]. Hypocalcemia diminishes myocardial contractility and results in left ventricular systolic dysfunction [2].

In this paper, we report a case of heart failure with hypocalcemia and primary hypoparathyroidism which was treated with vitamin D and calcium supplement.

CASE PRESENTATION

A 21-year-old female was admitted to our emergency department due to worsening dyspnea (NYHA class III) for seven days. Her past medical history was significant for primary hypoparathyroidism from six years ago, but she discontinued her regular medication (oral calcium and vitamin D) from three months. Moreover, she complained about numbness of both hands and feet for two months.

On physical examination, blood pressure was 100/65 mmHg, heart rate was 78 beats per minute, respiratory rate was 16 breaths per minute, and body temperature was 36.8°C. Chvostek's and Trousseau's signs were positive. On auscultation of the chest, there were coarse fine rales on the base of both lung fields, and grade III systolic murmur on apex and left sternal border were heard. The reminder of her physical examination was unremarkable.

Her electrocardiogram (ECG) showed normal sinus rhythm with T wave inversion in the precordial leads and prolonged QTc interval (520 msec). The transthoracic echocardiography demonstrated global hypokinesia of the LV with 13% left ventricular ejection fraction (EF), moderate diastolic dysfunction and mild mitral regurgitation (Fig 1). Chest radiography revealed cardiomegaly. Perfusion stress test revealed no signs of ischemia.

Laboratory studies revealed the following: magnesium 1.5 mg/dL (reference range: 1.6-3.0 mg/dL), albumin 4.2 g/dL (reference range: 3-5.5 mg/dL), corrected calcium 7 mg/dL (reference range: 8.6-10 mg/dL), phosphate 10.1 mg/dL (reference range: 2.5-5 mg/dL), and intact parathyroid hormone (PTH-I) 6 pg/mL (reference range: 15-65 pg/mL). CK-MB, cardiac troponin I, complete blood count, blood urea nitrogen (BUN), serum creatinine, blood glucose, Na+, K+, alanine aminotransferase (SGOT), aspartate aminotransferase (SGPT), alkaline phosphatase, bilirubin, T3, T4 and TSH were within normal ranges. Viral markers and full panel of rheumatology studies for autoimmune antibodies were all negative.

At the first night of her admission, she developed abnormal tonic movement, loss of consciousness and episode of polymorphic ventricular tachycardia (Fig 2), which was controlled with asynchronized 200 J shock. Treatment initiated with administration of furosemide, captopril, digitalis and spironolactone. In addition, calcium, magnesium and vitamin D were added to her drug regimen.

Following normalization of her calcium level, she was discharged after five days under the treatment of oral calcium, vitamin D_3, furosemide, carvedilol and captopril. Her ejection fraction at the time of discharge was 36%. She was planned for follow-up transthoracic echocardiography for evaluation of the cardiac function as well as for close observation of cardiology and endocrinology clinics.

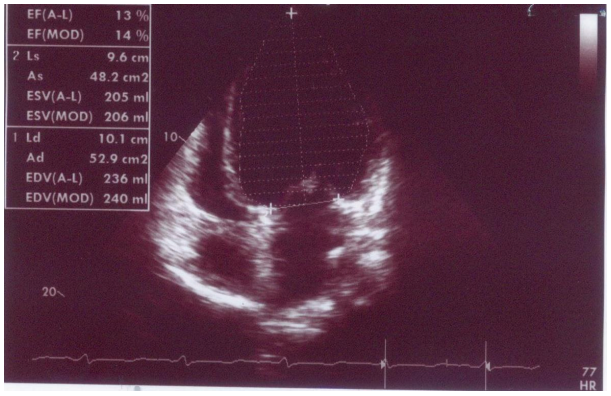

Figure 1: Transthoracic Echocardiography Demonstrated Global Hypokinesia of the LV with 13% of Left Ventricular Ejection Fraction, Which Was Measured by Biplane Simpson Method

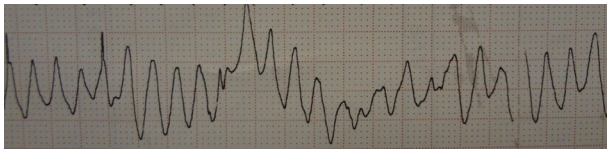

Figure 2: Polymorphic Ventricular Tachycardia Developed at the Night of the Admission

DISCUSSION

Hypocalcemia is a very unusual reversible cause of dilated cardiomyopathy, which can involve one or both ventricles. Hypocalcemia diminishes myocardial contractility, but the prevalence of congestive heart failure due to hypocalcemia is uncommon [2, 3]. Hypocalcemic cardiomyopathy due to hypoparathyroidism is a very atypical circumstance which is usually intractable to conventional therapy for cardiac failure, but responds satisfactorily to restoration of normocalcemia [4, 5].

Ionized calcium has an essential task for regulating myocardial contraction. During the cardiac action potential, ionized calcium enters the cells through depolarization-activated calcium channels. The entered ionized calcium elicits calcium release from the sarcoplasmic reticulum. Ca^{2+} binds to myofilaments proteins such as troponin C, commencing contraction of myocardium [6, 7].

Hypocalcemia results in not only heart failure, but also ST segment changes in ECG, which mimic acute myocardial ischemia and infarction; it may lead to life threatening cardiac arrhythmia like polymorphic ventricular tachycardia [8]. The hemodynamic and echocardiographic improvement of hypocalcemic cardiomyopathy could not be attained by usual medical treatments of heart failure [9].

The roles of calcium and vitamin D are pivotal in the treatment of hypocalcemic cardiomyopathy; but, it has been also emphasized on the impending role of parathyroid hormone (PTH) in preserving myocardial contractility [10]. Correction of serum level of calcium was not adequate for restitution of myocardial function. Rather, re-establishment of intracellular calcium level is thought to be more essential to returning myocardial function. It would take several months to normalized tissue calcium level [11]. Although cardiac function usually returns to normal status, there are some reports of persistent systolic dysfunction after vitamin D-calcium supplementation [12, 13]. There was no obvious cause for dilated cardiomyopathy in our case. Hypocalcemia was the lone probable cause, according to the pervious unusual case reports.

This case underscores the importance of biochemical abnormalities like hypocalcemia as a rare cause of secondary cardiomyopathy and emphasizes on the need for effective and immediate treatment of hypocalcemia and its related causes.

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CONFLICTS OF INTEREST

Authors declare that there is no conflict of interest for the present study.

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Int J Cardiovasc Pract. **Review Article**

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Acute Compartment Syndrome of the Right Lower Extremity Following Autologous Blood Transfusion: A Case Report

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Abstract

Compartment syndrome (CS) is an extremely rare complication during cardiac surgery and rare case reports have been linked to coronary artery bypass surgery.
We report one case of right lower extremity compartment syndrome (CS) following inadvertent blood transfusion through a catheter which was inserted into a vein in the related extremity. Forceful pushing of blood through a delicate vein led to rupture of the vein wall and subsequent extravasation of blood into the perivascular tissue as into an intra-compartment portion of the lower extremity.
Late detection of this complication led to compartement syndrome. The patient underwent emergency fasciotomy and concomitant removal of intra compartment and subcutaneous blood and fluids. After fasciotomy, the normal color of skin and pulse were recovered.

INTRODUCTION

Compartment syndrome (CS) is an extremely rare complication during cardiac surgery and rare case reports have been linked to coronary artery bypass surgery [1]. During harvesting of saphenous vein, some branches may be ruptured and then hidden in the subfascial space. These branches may bleed into the compartment space and lead to CS. Also, severe venous bleeding may be associated with subcutaneous hematoma which compresses the leg compartment [1]. Mild ischemia in this closet space is associated with edema and through a vicious cycle leads to CS. In these subjects, the first signs of compartment may be an excruciating extremity pain. However, if the case has not had a fast tract extubation, the golden time is over and amputation and neuromuscular deformity are devastating sequelae [2]. In rare cases, CS has been reported after anticoagulation therapy. In these cases, prescripting of anticoagulant druges to a patient with a congenital coagulation disorder was associated with bleeding in many sites such as extremity compartments [3]. Regardless of the etiology, if CS remains untreated, increased intracompartement pressure and devastating neuromuscular necrosis will result in sequela. We report a patient with CS of the right lower extremity following autologous blood transfusion after primary Bentall operation. This case, to our knowledge, was the first case of CS of the right lower extremity caused by a blood transfusion.

CASE PRESENTATION

A 55-year-old Iranian woman referred to our center with a history of dyspnea. Clinical and echocardiography evaluation showed severe and huge dilatation of ascending aorta and severe aortic insuficiency. She was scheduled for classic Bentall operation. In her medical history, no abnormal tendency to bleeding or other congenital or known hemophilia disorders were found. Her body mass index was 24 kg/m^2 and due to delicate vein wall and extensive subcutaneous fat, access to peripheral vein was difficult; however, a right central venous pressure (CVP) line and lower right extremity saphenous vein line were prepared for further transfusion. After midlinsternotomy, cardiopulmonary bypass was instituted and with moderate hypothermia, the ascending aorta just below the right subclavian vein was cross clamped and direct cardio-

plegin infusion was performed in both coronary ostium. With cardioplegin arrest, the aneurismal segment of the ascending aorta resected and with separation of both coronary artery bottoms, the classic Bentall operation was performed. Just after opening the aortic cross clamp, venous bleeding from aortic root was detected. Due to massive bleeding from venous network around the right coronary buttom and a hemoglobin drop to 7.5 g/dL, blood transfusion with manual syrange pump from both peripheral lines was started by the nurses and the aortic root was packed with surgical sponges. Approximately 30 minutes following packing of the aortic root and blood transfusion, the patient was still hypotensive. At this time, anesthesiologist detected a deformity and rigidity in patient's right leg. It was deformed by 70 degrees flexion, was severely edematous from 10 cm upper the knee to the finger tips. Acral part of the fingers had cyanosis and multiple blisters were detected in the skin and pulse was not detected in the tibia or ulnar arteries. On palpation, both the volar and dorsal aspects of the leg were severely firm and rigid. The distal pulse was not detected by Doppler ultrasound. At that time, the subject had received 700 mL of packed blood cell and 2000 mL normal saline through a 16-gauge venous catheter inserted preoperatively in saphenous vein in the right lower leg. Retrospectely evaluating the situation, we found that the nurse sensed a resistance when she infused the packed cells through the intravenous catheter which was initially placed in the saphenous vein, but she thought that a mechanical problem in syringes was causing this resistance. It seems that the whole transfusion and normal saline were inadvertently infused into the extra venous interstitial tissue. CS was confirmed and extended fasciotomy was performed. Approximately 700 mL of hematoma was removed upon opening of the subcutaneous tissue and release of the superficial fascia, which was suspicious as the cause of CS. The deep fascia was noted to be tight and was released, and the dorsal compartment was released through a small window in the interosseous membrane. The fasciotomy incision was approximated using separate proline sutures. Immediately after fasciotomy, the pulse returned to distal arteries, cyanosis was relived and muscle consistency became soft and normal. Examination in the post-extubation period showed no pain with normal passive range of motion of fingers; however, she had paresthesias of medial aspect of the leg (Fig 1). At the 15th day of the postoperative period, she had a residual strength deficit. The patient was discharged from the hospital on the 20th day postoperative. The patient was examined one, two and three weeks after discharge from the hospital. The incisional leg wound was healed at that time without the presence of erythema or drainage. However, the case continued to have a residual paresthesia on medial aspect of the right thumb at that time.

DISCUSSION

In cardiac surgery cases after general anesthesia, symptoms such as pain have not been found in CS and the first sign may be resistance in syringes used for pushing blood in these emerging patients. Unfortunately, if this issue is linked to mechanical or structural problems of syringes, the anesthesiologist and nurse may be heedless of this major complication and continue the forceful transfusion. With rupture of the vein wall and continuation of transfusion, especially in a full anticoagulation state, more subcuataneous and intra-compartment space get opened for further inadvertent transfusion. In this stage, the resistance to infusion reduces and through a vicious cycle, a copious amount of fluids may be infused into subcutaneous and intra-compartment of the extremity. In this stage in our study, the skin blister with an abnormal flexion position in the related extremity appeared. Due to coverage of extremity in non-coronary cases, the flexion of extremities may be a late and single sign of this rare complication [4]. Early detection of CS of any etiology is important because it can lead to irreversible injury if remained untreated. Calf is the rarest site of CS amongst the four extremities. Pain is the most important symptom in awake cases; also, pain with passive extension of fingers has been exhibited to be the most sensitive sign of CS. Detection of a palpable tibial pulse is equivocal in the diagnosis of CS in complicated cases [5]. Functional impairment of muscles was observed from 120 minutes to 240 minutes of ischemia; but in nerve tissue, abnormal function has been seen after 30 minutes. Matsen et al. exhibited that if fasciotomy is delayed for 720 minutes or more, only 7% could have a normal neuromuscular function vs. 70% who will have on time fasciotomy within 720 minutes [6]. The etiology of CS in our case was unique; our hypothesis is that there was a technical problem in catheter insertion that caused a malfunction in catheter. However, misplacement of the catheter into extra venous tissue leads to extravasation of blood to the soft tissue. The catheter could have been placed through the vein and into the subcutaneous and superficial fascial compartment. It is noteworthy that copious amount of hematoma (700 mL) was removed after the release of the superficial fascia. In careful literature search, we found no previous reported studies that described calf CS from such a small amount of extravasated fluid. However, intravenous catheter is a common cause of extravasation of fluids in forearm area, but has rarely led to CS, because the forearm veins have an extra-compartmental position. Kagel et al. showed one forearm CS of 67 intravenous catheter misplacement during a 3-year period [7]. Our case confirmed the importance of avoiding a placement of catheter in a lower extremity vein in cardiac surgery cases where lower extremity is covered; however, intra-compartmental pressures exam is a good option in a cardiac case where the risk of CS is high. Another risk factor for occurrence of CS in our case was prolonged postoperative hypotension. Hypotension is believed to be a predisposing factor to CS [8]. This case highlighted the importance of possible intravenous catheter misplacement or rupture during blood infusion. This case also showed that despite the presence of an extensive network of vein that connects the superficial veins to intra-compartment parts, extravasation of large amounts of fluid into the superficial tissue with compression of lower compartment can potentially lead to CS.

CONFLICTS OF INTEREST

There is no conflict of interest for the present study.

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