Journal of Cardiology 73 (2019) 358–362

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

# Risk factors of non-sustained ventricular tachycardia by technetium-perfusion imaging in patients with coronary artery lesions caused by Kawasaki disease

Tadaaki Abe (MD, PhD)[a,*], Etsuko Tsuda (MD, PhD)[a], Hisashi Sugiyama (MD, PhD)[a], Keisuke Kiso (MD, PhD)[b], Osamu Yamada (MD)[a]

[a] Department of Pediatric Cardiology, National Cerebral and Cardiovascular Center, Osaka, Japan
[b] Department of Radiology, National Cerebral and Cardiovascular Center, Osaka, Japan

ARTICLE INFO

*Article history:*
Received 16 April 2018
Received in revised form 26 August 2018
Accepted 28 October 2018
Available online 31 December 2018

*Keywords:*
Kawasaki disease
Coronary artery lesion
Extent score
Non-sustained ventricular tachycardia
Myocardial perfusion imaging

ABSTRACT

*Background:* Sudden death can occur in some patients with non-sustained ventricular tachycardia (NSVT) after myocardial infarction (MI) in those with coronary artery lesions (CAL) caused by Kawasaki disease (KD). The aim of this study was to determine the risk factors for NSVT in the late period after KD by technetium-99m-tetrofosmin myocardial perfusion imaging (MPI).
*Methods:* We retrospectively analyzed the relation between the appearance of NSVT and the findings in MPI single-photon-emission computed tomography (SPECT) in 75 patients (55 males and 20 females) who had had CAL caused by KD. All the patients had undergone MPI and 24-h Holter electrocardiogram at the same time between 2003 and 2012. The age at MPI ranged from 2 to 44 years (median 19 years), and the time from the onset of KD to MPI ranged from 1 to 44 years (median 18 years). We evaluated extent score (ES), summed rest score (SRS), summed stress score (SSS), summed difference score (SDS), and left ventricular ejection fraction (LVEF) by quantitative gated SPECT software. We analyzed which factors related to NSVT using multivariate logistic regression. Further, we calculated the cut-off point for NSVT using receiver operating characteristic curve.
*Results:* The affecting factors were ES (OR, 0.63, 95%CI, 0.35–0.92, $p = 0.013$) and the interval from the onset of KD to MPI (OR, 0.82, 95%CI, 0.69–0.96, $p = 0.004$). The cut-off points for ES and the interval from the onset of KD were 11% (AUC, 0.931, $p < 0.001$) and 18 years (AUC, 0.732, $p = 0.007$), respectively.
*Conclusions:* ES is the strongest parameter for predicting NSVT in the late period. In patients with post-KD, adolescence and young adults with ES $\geq$11% are at risk of fatal ventricular arrhythmia.


## Introduction

Coronary artery lesions (CAL) caused by Kawasaki disease (KD) have been the most commonly associated complications that can lead to ischemic heart disease including myocardial infarction (MI) or sudden death [1,2]. Several articles describing adult patients who had fatal ventricular tachycardia (VT) many years after presumed KD have been published [3]. Further, we reported that sudden death can occur in patients with non-sustained ventricular tachycardia (NSVT) and a low left ventricular ejection fraction after MI [4]. A means of predicting risk of NSVT would be useful in the follow-up and the management of this population. Technetium-99m-tetrofosmin myocardial perfusion imaging (MPI) is promising in this respect. MPI has been performed in patients with coronary artery disease, and myocardial ischemia, perfusion defects, and low left ventricular function. Further, single-photon emission computed tomography (SPECT) score such as summed stress score in MPI predicts cardiac events and the prognosis of the patient with coronary artery diseases, and they have become major determinants for risk stratification of future cardiac events [5–7]. We investigated the factors related to the occurrence of NSVT in patients with CAL after KD using MPI.

## Materials and methods

### Study population

We retrospectively analyzed 75 patients (55 males and 20 females) with CAL caused by KD who had undergone gated

* Corresponding author at: Department of Pediatrics, Niigata City General Hospital, 463-7, Shumoku, Chuo-ku, Niigata City 950-1197, Japan.
*E-mail address:* abechin@hosp.niigata.niigata.jp (T. Abe).

https://doi.org/10.1016/j.jjcc.2018.12.007
0914-5087/

MPI-SPECT at rest and under stress within a day and 24-hour Holter electrocardiogram within one year of the MPI between 2003 and 2012 in the National Cerebral and Cardiovascular Center of Japan. The age at the onset of KD ranged from 2 months to 12 years (median 17 months). All 75 patients had the diagnosis of CAL confirmed by selective coronary angiographies. They had had no cardiac event between MPI and 24-hour Holter electrocardiogram. The periods from the onset of KD to MPI ranged from 9 months to 44 years (median 18 years). Of the 75 patients, 16 (21%) had had previous MI caused by KD. Three patients had had repetitive MI. The diagnosis of MI was based on symptoms including chest pain, changes in a 12-lead electrocardiogram, and myocardial enzyme elevation [4]. Asymptomatic coronary occlusion and segmental stenosis found unexpectedly by CAG were not included as MI in this study. The interval from the onset of KD to the initial MI ranged from 2 months to 8 years with a median of 1 year, and the interval from MI to MPI was 6 months to 27 years with a median of 15 years. Twenty-seven patients (36%) underwent coronary artery bypass grafting (CABG). There was no death in this population during our study period. Beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and potassium channel blockers were administered in 20 (27%), 11 (15%), 2 (3%), and 6 (8%), respectively.

*Technetium-99m-tetrofosmin myocardial perfusion single photon emission computed tomography*

All the patients underwent gated MPI-SPECT with technetium-99m-tetrofosmin administered by intravenous injection at rest and stress in a day. Sixty-six patients underwent exercise stress, and nine patients did drug stress. In cases with exercise stress, patients pedaled a bicycle ergometer for about 7 min. The exercise stress was controlled by the bicycle pedal heaviness according to patient's physical strength. Endpoints of the exercise stress included achievement of 85% of age-adjusted maximum heart rate, more than 2 mm ST segment elevation, anginal attack such as chest pain, and physical limitation. In cases with drug stress, dipyridamole of 0.56 mg/kg was administered over 4 min. The total dose of technetium-99m was decided depending on body weight and age, and ranged from 296-MBq to 740-MBq. One-quarter of the total dose was injected at stress, and about 3 h later, the remaining three-quarters was injected at rest. Approximately one hour after each injection, SPECT was performed using a dual-head angular rotating γ-camera (VERTEX+MCD; ADAC Laboratories located in 540 Alder Dr. Milpitas, CA 95035, USA) equipped with a low-energy general-purpose collimator. Image acquisition parameters were 180° (30 steps; 6° per step) using 64 × 64 matrix and 20% main window centered at the photopeak energy of technetium-99m (140 keV). At each projection, a total of 8 individual electrocardiographic gated frames or cardiac cycles were acquired (50 beats per step).

We evaluated extent scores (ES), summed rest scores (SRS), and left ventricular ejection fractions (LVEF) at rest, and also evaluated summed stress scores (SSS) and summed difference scores (SDS) at stress. The definition and cases of ES are shown, respectively (Figs. 1 and 2). ES was the ratio of hypoperfusion area less than 2 standard deviations to total area in polar map [8]. Actually, ES was automatically calculated by quantitative perfusion SPECT software developed by Cedars-Sinai Medical Center located in 8700 Beverly Blvd, Los Angeles, CA 90048, USA.

LVEF was automatically measured from the reconstructed short-axis images by applying quantitative gated SPECT software also developed by Cedars-Sinai Medical Center. The software operates in 3-dimensional space. It distinguishes between endocardial and epicardial surfaces for all gating intervals in the cardiac cycle. And then it calculates the left ventricular cavity volumes, and derives the global LVEF from the end-diastolic and end-systolic volume without operator interaction.

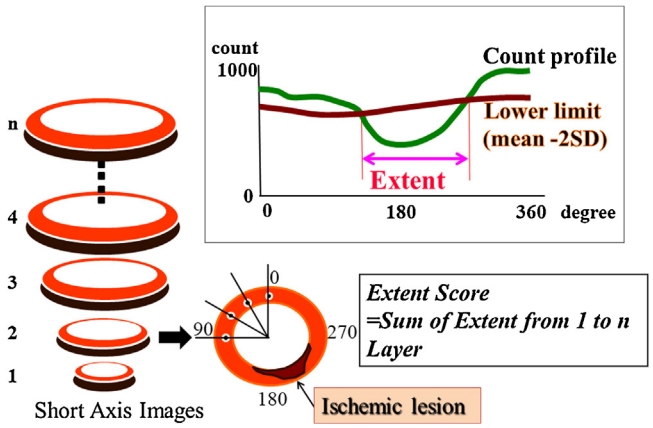



**Fig. 1.** Calculation of extent score. In each short-axis image, the ischemic lesions were analyzed in the circumferential area. Hypoperfusion less than 2 standard deviation from the mean was defined as an ischemic lesion, and its dimension was extent. Summation of the extent from apical layer to basal layer was defined as an extent score [8].

We also assessed SRS as a quantification of myocardial perfusion defect at rest using a polar map consisting of 20 segments. An extent of perfusion defect on each segment was automatically scored on a scale ranging from 0 to 4 points compared with that of normal perfusion. Zero points and 4 points were equivalent to full perfusion and no perfusion, respectively. SRS was the total of each segment score. These scores were also automatically calculated by the quantitative perfusion SPECT software. SSS at stress was calculated as the same as SRS at rest, and SDS was the difference between SSS and SRS.

*24-hour Holter electrocardiogram*

Two-channel 24-hour electrocardiogram recordings were recorded. We assessed ventricular arrhythmia by computer with manual review. Ventricular arrhythmias were classified as isolated premature ventricular contraction (PVC), couplets, NSVT, and VT. NSVT was defined as self-terminating bursts of 3 beats or more consecutive PVCs lasting less than 30 s.

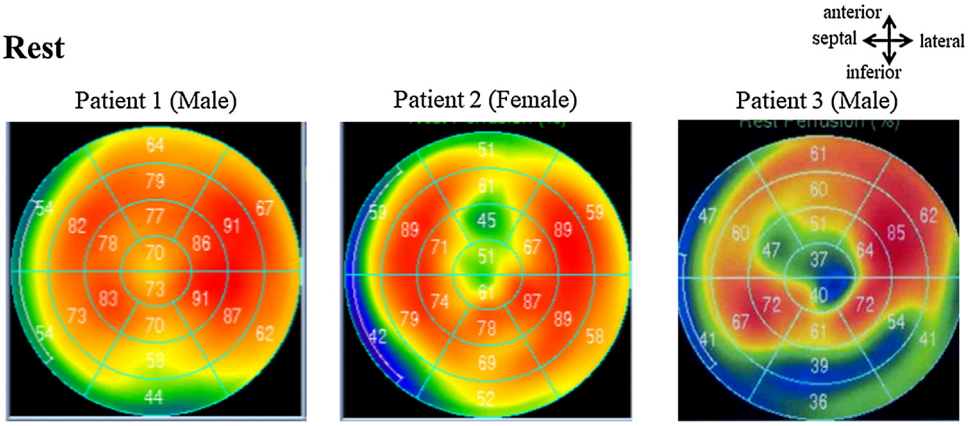
We divided the patients into two groups. Group one was the patients with NSVT, and group two was the non-NSVT patients. Patients who had had VT before were included in the NSVT group. We investigated the risk factors for the occurrence of NSVT by univariate and multivariate logistic analyses. Further, we investigated the relation between ES and ventricular arrhythmia. Furthermore, we calculated the cut-off points of influencing factors about the occurrence of NSVT using receiver operating characteristic (ROC) curve.

*Statistical analysis*

JMP10 (SAS Institute Inc., Cary, NC, USA) was used as statistical software. We considered statistical significance at $p < 0.05$.

## Results

The results of ventricular arrhythmia were as follows. No PVC, isolated PVC, and couplets were detected in 32 patients (43%), 21 patients (28%), and 12 patients (16%), respectively. NSVT was detected in 10 patients (13%). Two patients who had undergone implantable cardioverter-defibrillator (ICD) because of VT were included in NSVT group. The numbers of non-NSVT and NSVT group




| | | | |
|---|---|---|---|
| Age at MPI | 9 years | 24 years | 44 years |
| Age at acute KD | 4 years | 4 years | 10 months |
| Previous MI | Inferior (5 y) | Inferior (4y), Anteroseptal ( 5y) | none |
| Extent Score | 3% | 22% | 24% |
| SRS | 0 | 12 | 14 |
| LVEF (QGS) | 72% | 49% | 39% |
| Arrhythmia | PVC | NSVT | NSVT/VT |

**Fig. 2.** The findings in $^{99m}$Tc-myocardial perfusion imaging. *Abbreviations*: MPI, myocardial perfusion imaging; KD, Kawasaki disease; MI, myocardial infarction; SRS, summed rest score; LVEF, left ventricular ejection fraction; QGS, quantitative gated single-photon emission computed tomography; NSVT, non-sustained ventricular tachycardia; VT, ventricular tachycardia; PVC, premature ventricular contraction.

were 65 patients and 10 patients, respectively. The characteristics and the results in MPI are shown in Table 1.

The parameters for the occurrence of NSVT by the univariate and multivariate logistic analyses are shown in Table 2. In the univariate analysis, the significant parameters were the interval from KD to MPI (OR, 0.91, 95%CI, 0.84–0.98, $p = 0.007$), previous CABG (OR, 0.19, 95%CI, 0.04–0.76, $p = 0.018$), the use of antiarrhythmic agents (OR, 0.06, 95%CI, 0.01–0.26, $p < 0.001$), ES (OR, 0.82, 95%CI, 0.73–0.90, $p < 0.001$), quantitative gated SPECT-LVEF (OR, 1.10, 95%CI, 1.04–1.19, $p = 0.001$), SRS (OR, 0.79, 95%CI, 0.68–0.90, $p < 0.001$), and SSS (OR, 0.83, 95%CI, 0.73–0.91, $p < 0.001$). In the multivariate analysis, the significant parameters for the occurrence of NSVT were the interval from KD to MPI (OR, 0.85, 95%CI, 0.69–0.96, $p = 0.004$) and ES (OR, 0.63, 95%CI, 0.35–0.92, $p = 0.013$).

We investigated the relation between ES and ventricular arrhythmia. The results are shown in Fig. 3. The higher ES and the longer interval from the onset of KD, the more NSVT appeared.

We analyzed the cut-off points of ES and the interval from the onset of KD (Table 3). The cut-off points for ES and the interval from the onset of KD were 11% (AUC, 0.931, $p < 0.001$) and 18 years (AUC, 0.732, $p = 0.007$), respectively.

**Table 1**
Characteristics and results of MPI in non-NSVT and NSVT patients.

| | *Non-NSVT | NSVT |
|---|---|---|
| | Median (range) | |
| Patient ($n$) | 65 | 10 |
| Male, $n$ (%) | 50 (77%) | 5 (50%) |
| Age at MPI (years) | 19 (2–40) | 31 (18–45) |
| Interval from KD to MPI (years) | 17 (1–37) | 26 (12–44) |
| Previous myocardial infarction, $n$ (%) | 12 (18%) | 4 (40%) |
| Previous CABG, $n$ (%) | 20 (31%) | 7 (70%) |
| Antiarrhythmic agent, $n$ (%) | 12 (18%) | 8 (80%) |
| Extent score | 4 (0–31) | 24 (7–43) |
| QGS-LVEF (%) | 65 (33–98) | 53 (23–70) |
| Summed rest score | 0 (0–21) | 11 (1–41) |
| Summed stress score | 5 (0–27) | 16 (4–41) |
| Summed difference score | 3 (0–11) | 4 (0–7) |

NSVT, non-sustained ventricular tachycardia; MPI, myocardial perfusion imaging; KD, Kawasaki disease; CABG, coronary artery bypass grafting; QGS, quantitative gated single-photon emission computed tomography; LVEF, left ventricular ejection fraction.
* Non-NSVT, no premature ventricular contraction, isolated premature ventricular contraction and couplets.

## Discussion

This study clarified that ES in MPI and the interval from the onset of KD were significantly related to the occurrence of NSVT in patients with CAL caused by KD. We hypothesized that the extension of myocardial involvement and the lasting time after the myocardial scarring could have an effect on the incidence of NSVT in this population. In this study, ES was a more important risk factor for NSVT than SRS. It suggests that NSVT is more dependent on the extension of a myocardial injury rather than the depth of that, because ES reflects only the area of myocardial involvement, whereas SRS is a combined score that integrates both the area and the depth. For instance, a single segment of full thickness MI will generate the same SRS as 4 segments of very mild scarring, however, ES alone can differentiate between these two scenarios better and this may be the reason why it can be better at predicting ventricular arrhythmia. One of the mechanisms for VT in the late period after MI is reentry between fibrosis developing in the infarct area and the normal myocardium [9]. Therefore, it seems that the greater the borderline area composed of bundles of viable myocytes embedded in regional scars spread, the higher the reentrant ventricular arrhythmia can occur.

In adult patients with post-MI caused by atherosclerosis, NSVT is confirmed as an independent risk factor for total and sudden death following the acute event [10,11]. Furthermore a low LVEF with NSVT is also a risk factor in the late period after MI [12,13]. It is

**Table 2**
The parameters for the occurrence of NSVT.

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| Variables | Odds ratio | 95%CI | *p* value | Odds ratio | 95%CI | *p* value |
| Interval from KD to MPI | 0.91 | 0.84–0.98 | 0.007 | 0.85 | 0.69–0.96 | 0.004 |
| Previous myocardial infarction | 0.34 | 0.08–1.50 | 0.15 | | | |
| Previous CABG | 0.19 | 0.04–0.76 | 0.018 | | | |
| Antiarrhythmic agent* | 0.06 | 0.01–0.26 | <0.001 | | | |
| Extent score | 0.82 | 0.73–0.90 | <0.001 | 0.63 | 0.35–0.92 | 0.013 |
| QGS-LVEF | 1.10 | 1.04–1.19 | 0.001 | | | |
| Summed rest score | 0.79 | 0.68–0.90 | <0.001 | | | |
| Summed stress score | 0.83 | 0.73–0.91 | <0.001 | | | |
| Summed difference score | 0.95 | 0.74–1.24 | 0.68 | | | |

NSVT, non-sustained ventricular tachycardia; CI, confidence interval; KD, Kawasaki disease; MPI, myocardial perfusion imaging; CABG, coronary artery bypass grafting; QGS, quantitative gated single-photon emission computed tomography; LVEF, left ventricular ejection fraction.
* Beta-blocker and potassium channel blocker.

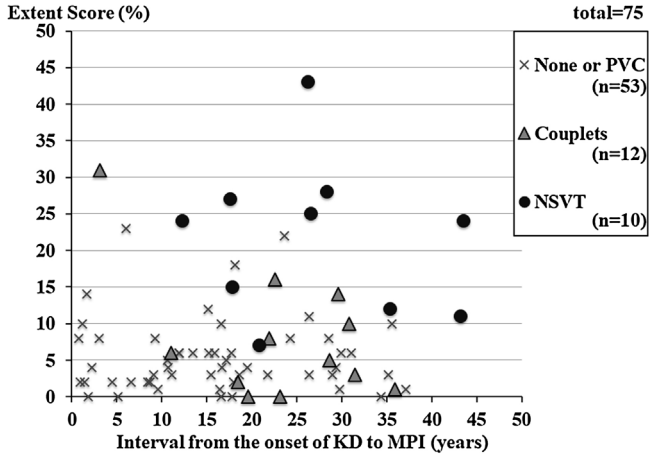



**Fig. 3.** Relation between extent score and ventricular arrhythmia. Most of non-sustained ventricular tachycardia group was existed in the right upper corner. *Abbreviations*: MPI, myocardial perfusion imaging; KD, Kawasaki disease; NSVT, non-sustained ventricular tachycardia; PVC, premature ventricular contraction.

known that SPECT scores in MPI are good predictors of the prognosis in patients with coronary artery disease [14,15]. We conclude that the predictors of prognosis by SPECT scores in MPI may reflect the occurrence of fatal ventricular arrhythmia due to myocardial involvement rather than coronary artery events such as MI. On the other hand, late gadolinium-enhanced cardiac magnetic resonance has excellent sensitivity and specificity for detecting myocardial scars and quantifying the core scar and border zone [16]. Late gadolinium-enhanced cardiac magnetic resonance has been shown to detect ventricular tachycardia-associated scars. Therefore, a magnetic resonance study reported that late gadolinium-enhanced cardiac magnetic resonance has become a useful tool for predicting cardiac events [17]. ES in MPI may be also corresponding to late gadolinium-enhanced cardiac magnetic resonance. Although isotope examination has demerits of the risk of radiation and the expensive cost, it has merits that the examination is possible in patients with either device implantation or allergy to contrast.

**Table 3**
Cut-off points of the parameters.

| Variables | Cut-off points | AUC | *p* value |
|---|---|---|---|
| Interval from KD to MPI | 18 years | 0.732 | 0.007 |
| Extent score | 11% | 0.931 | <0.001 |

MPI, myocardial perfusion imaging; KD, Kawasaki disease; AUC, area under the curve.

Usually, the appearance of arrhythmia in children is rare except for hereditary arrhythmia caused by genetic syndrome. The prevalence of arrhythmia increases with aging, because most of the occurrence of arrhythmia is related to the myocardial involvement. It is speculated that the reentry in the late period after MI occurs for many years in children with CAL caused by KD. Therefore, the interval from the onset of KD can become the other important factor for the occurrence of NSVT in this population. Strictly, it is the interval from the exposure of myocardial involvement. Myocardial involvement caused by KD can be also induced by asymptomatic coronary artery complete occlusion, not only symptomatic myocardial infarction.

From the results of this study, we must take care of fatal ventricular arrhythmia in adolescence and young adult patients with ES $\geq$ 11%. Myocardial involvement due to coronary artery involvement in this population must be minimized. The cut-off points in two significant risk factors are of clinical importance to identify these high-risk patients because optimal medical and device therapy substantially lower the risk. Antiarrhythmic agents such as amiodarone in patients with NSVT may be needed. Further, in some patients with low LVEF and NSVT, ICD might be a candidate to prevent sudden deaths due to fatal ventricular arrhythmia in the future.

### *Study limitations*

Although the left ventricle in the imaging of MPI is detected, the right ventricle cannot be detected in ordinary cases. Therefore, it is unknown what is the relation of the findings of MPI and the occurrence of PVC originating from the right ventricle. That is a limitation in this study.

## Conclusion

The appearance of NSVT can occur in patients with myocardial involvement more than 11% of ES in the late period more than 18 years after the onset of KD. ES is the strongest parameter of predicting NSVT in the late period.

## Funding

This research received no grant from any funding agency in the public, commercial, or not-for-profit sectors.

## Conflict of interest

The authors declare that there is no conflict of interest.

## Acknowledgments

We thank Professor Peter and Setsuko Olley for their kind English language consultation.

## References

[1] Kato H, Sugimura T, Akagi T, Sato N, Hashino K, Maeno Y, et al. Long-term consequences of Kawasaki disease: a 10- to 21-year follow up study of 594 patients. Circulation 1996;94:1379–85.
[2] Newburger JW, Takahashi M, Burns JC. Kawasaki disease. J Am Coll Cardiol 2016;67:1738–49.
[3] Yagi S, Tsuda E, Shimizu W, Kurita T, Seguchi O, Nonogi H, et al. Two adults requiring implantable defibrillators because of ventricular tachycardia and left ventricular dysfunction caused by presumed Kawasaki disease. Circ J 2005;69:870–4.
[4] Tsuda E, Hayashi T, Matsuo O, Abe T, Sugiyama H, Yamada O. The 30-year outcome for patients after myocardial infarction due to coronary artery lesions caused by Kawasaki disease. Pediatr Cardiol 2011;32:176–82.
[5] Nakajima K, Matsuo S, Okuda K, Wakabayashi H, Tsukamoto K, Nishimura T. Estimation of cardiac event risk by gated myocardial perfusion imaging and quantitative scoring methods based on a Multi-Center J-ACCESS Database. Circ J 2011;75:2417–23.
[6] Nakata T, Hashimoto A, Matsuki T, Yoshinaga K, Tsukamoto K, Tamaki N. Prognostic value of automated SPECT scoring system for coronary artery disease in stress myocardial perfusion and fatty acid metabolism imaging. Int J Cardiovasc Imaging 2013;29:253–62.
[7] Aburadini I, Usuda K, Sumiya H, Sakagami S, Kiyokawa H, Matsuo S, et al. Ability of the prognostic model of J-ACCESS study to predict cardiac events in a clinical setting: the APPROACH study. J Cardiol 2018;72:81–5.
[8] Imai K, Shibata T, Ogawa H, Horie T. Relationship between exercise induced ischemia and left ventricular dysfunction; simultaneous assessment of perfusion and function images with $^{99m}$Tc-tetrofosmin myocardial scintigraphy. Kaku Igaku 1996;33:981–9.
[9] Pogwizd SM. Focal mechanisms underlying ventricular tachycardia during prolonged ischemic cardiomyopathy. Circulation 1994;90:1441–58.
[10] Maggioni AP, Zuanetti G, Franzosi MG, Rovelli F, Santoro E, Stazewsky L, et al. Prevalence and prognostic significance of ventricular arrhythmias after acute myocardial infarction in the fibrinolytic era GISSI-2 results. Circulation 1993;87:312–22.
[11] Atchley AE, Iskandrian AE, Bensimhon D, Kitzman DW, Shaw LK, Pagnanelli RA, et al. Relationship of technetium-99m tetrofosmin-gated rest single-photon emission computed tomography myocardial perfusion imaging to death and hospitalization in heart failure patients: results from the nuclear ancillary study of the HF-ACTION trial. Am Heart J 2011;161:1038–45.
[12] Bigger Jr JT, Fleiss JL, Rolnitzky LM. Prevalence, characteristics and significance of ventricular tachycardia detected by 24-hour continuous electrocardiographic recordings in the late hospital phase of acute myocardial infarction. Am J Cardiol 1986;58:1151–60.
[13] Cheema AN, Sheu K, Parker M, Kadish AH, Goldberger JJ. Nonsustained ventricular tachycardia in the setting of acute myocardial infarction: tachycardia characteristics and their prognostic implications. Circulation 1998;98:2030–6.
[14] Jain D, Lessig H, Patel R, Sandler L, Weiland F, Edell SL, et al. Influence of $^{99m}$Tc-tetrofosmin SPECT myocardial perfusion imaging on the prediction of future adverse cardiac events. J Nucl Cardiol 2009;16:540–8.
[15] Cheong BY, Muthupillai R, Wilson JM, Sung A, Huber S, Amin S, et al. Prognostic significance of delayed-enhancement magnetic resonance imaging: survival of 857 patients with and without left ventricular dysfunction. Circulation 2009;120:2069–76.
[16] Roes SD, Borleffs CJ, van der Geest RJ, Westenberg JJ, Marsan NA, Kaandorp TA, et al. Infarct tissue heterogeneity assessed with contrast-enhanced MRI predicts spontaneous ventricular arrhythmia in patients with ischemic cardiomyopathy and implantable cardioverter-defibrillator. Circ Cardivasc Imaging 2009;2:183–90.
[17] Wijnmaalen AP, van der Geest RJ, van Huls van Taxis CF, Siebelink HM, Kroft LJ, Bax JJ, et al. Head-to-head comparison of contrast-enhanced magnetic resonance imaging and electroanatomical voltage mapping to assess post-infarct scar characteristics in patients with ventricular tachycardias: real-time image integration and reversed registration. Eur Heart J 2011;32:104–14.