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Original Article

Contributing Factors and Ultrasonographic Findings of Fresh and Chronic Mixed Venous Thrombosis in Post-Earthquake: A Cross-Sectional Study

Hiromasa Tsubouchi [a], Hidenori Onishi [b *], Shinsaku Ueda [c], Muneichi Shibata [d], Soichi Enomoto [e], Fumie Maeda [f], Takeshi Hirobe [g], Hiroshi Chiba [h], Yoshitaka Ota [i], Satoshi Daitoku [j], Tami Yamamoto [k], Kazuhiro Sasaki [l], Kazuhiko Hanzawa [m], Yutaka Kai [n], Yoichiro Hashimoto [o], Tadanori Hamano [e], Yasunari Nakamoto [e], Hiroyuki Hayashi [p], Osamu Yamamura [b]

[a] *Department of Radiotechnology, Fukui-Ken Saiseikai Hospital, Fukui, Japan,* [b] *Department of Community Medicine, Faculty of Medical Science, University of Fukui, Fukui, Japan,* [c] *Department of Thoracic Surgery, Ishinomaki Red Cross Hospital, Miyagi, Japan,* [d] *Department of Cardiology, Mackay Base Hospital, Mackay, Australia,* [e] *Second Department of Internal Medicine, Faculty of Medical Science, University of Fukui, Fukui, Japan,* [f] *Department of Clinical Laboratory, University of Fukui Hospital, Fukui, Japan,* [g] *Department of Clinical Laboratory, Fukui Prefectural Hospital, Fukui, Japan,* [h] *Division of Clinical Laboratory, Morioka Municipal Hospital, Iwate, Japan,* [i] *Department of Radiology, Iwate Medical University Hospital, Iwate, Japan,* [j] *Department of Radiological Technology, Faculty of Medical Technology, Niigata University of Health and Welfare, Niigata, Japan,* [k] *Department of Clinical Laboratory, Saiseikai Kumamoto Hospital, Kumamoto, Japan,* [l] *Department of Neurology, Morioka Municipal Hospital, Iwate, Japan,* [m] *Department of Respiratory Surgery, Graduate School of Medicine, University of Niigata, Niigata, Japan,* [n] *Department of Neurosurgery, Aso Medical Center, Kumamoto, Japan,* [o] *Department of Neurology, Kumamoto City Hospital, Kumamoto, Japan,* [p] *Department of Emergency Medicine and General Medicine, University of Fukui Hospital, Fukui, Japan*

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SUMMARY

Background: Pulmonary embolism may develop due to unfavorable postearthquake living conditions and result in related deaths. Here we investigated the factors and characteristic ultrasonographic imaging features associated with fresh and chronic mixed venous thrombosis (FCMVT) in the calf of middle-aged and elderly people after a major disaster.
Methods: We included 791 individuals who underwent screening for deep venous thrombosis (DVT). After obtaining written informed consent from all participants, we retrospectively investigated the factors contributing to FCMVT and characteristic findings of FCMVT in the calf based on interviews and ultrasonography results.
Results: Patients with FCMVT were significantly older and had knee osteoarthritis significantly more frequently than patients with DVT and patients without thrombosis. Characteristic ultrasonographic images of FCMVT showed thrombi with mixed echogenicity. We referred to these characteristic ultrasonographic features as "the blowfish sign."
Conclusion: In middle-aged and elderly people, a higher prevalence of knee osteoarthritis was associated with FCMVT. FCMVT in the calf showed a characteristic finding termed as the blowfish sign.

1. Introduction

After the Chuetsu Earthquake in the Niigata Prefecture in October 2004, cases of fatality because of pulmonary embolism (PE) attributed to spending nights in a car were reported, and since then, postearthquake venous thromboembolism (VTE) has attracted attention.[1] After the Great East Japan Earthquake in March 2011 and the Kumamoto Earthquake in April 2016, a high incidence of deep venous thrombosis (DVT) was reported in shelters.[2–5] Other research indicated that DVT persists even after living conditions improve after individuals move from shelters to temporary housing.[3,6,7] Due to drastic changes in the living environment of middle-aged and elderly people, the onset of cardiovascular diseases, inactivity, and disaster-related diseases, including DVT, has attracted attention owing to the decline in mental and physical functions.[8,9] After a major disaster, we conducted lower-extremity venous ultrasonography screening of evacuees in temporary housing and encountered cases of fresh and chronic mixed venous thrombosis (FCMVT).[10] Ro et al. reported that 85% of autopsied patients who died of acute PE had a mixture of fresh and organized thrombi.[11] Therefore, the possibility of VTE recurrence in individuals who have postearthquake DVT of the calf cannot be denied, and long-term attention is needed. However, there are no reports showing the contributing factors or characteristic ultrasonographic images of FCMVT in middle-aged and elderly people after a major disaster. We investigated the factors that contribute to FCMVT and characteristic ultrasonographic imaging features of FCMVT in middle-aged and elderly people after a major disaster and report the results here.

2. Methods

2.1. Study subjects

Study participants lived in temporary housing or reconstructed housing in Watari-town, Miyagi Prefecture, during September 2012

* Corresponding author. 23-3 Matsuokashimoaizuki, Eiheiji-cho, Yoshida-gun, Fukui, Japan.
E-mail address: o-hide68@u-fukui.ac.jp (H. Onishi)

(i.e., 18th month after the disaster), September 2013 (i.e., 30th month after the disaster), November 2014 (i.e., 44th month after the disaster), and October 2015 (i.e., 55th month after the disaster) as well as in Minami Aso-village or Nishihara-village, Kumamoto Prefecture, during December 2016 (i.e., 8th month after the disaster), November 2017 (i.e., 19th month after the disaster), and November 2018 (i.e., 31th month after the disaster). Of the 835 middle-aged and elderly (age, ≥ 50 years) survivors who lived in temporary housing or reconstructed housing and requested DVT screening, 791 (200 men, 591 women; mean age, 72.1 ± 8.6 years) were included in the study. We excluded 44 participants with missing data (age and unmeasured soleus vein diameter).

2.2. Methods and measurements

The gathering places of the temporary housing facilities of Yamamoto-town and Watari-town, Watari-gun, Miyagi Prefecture, and Minami Aso-village and Nishihara-village, Kumamoto Prefecture, were used to perform DVT screening. We explained the aim and importance of the ultrasonographic screening for VTE prevention and obtained written consent from all disaster victims. In the interviews conducted before the screening, we inquired about age, sex, living conditions after the disaster, underlying diseases, and lifestyle habits (smoking and drinking). The underlying diseases (dyslipidemia, diabetes mellitus, heart disease, and hypertension) of the subjects were reported based on their answers to the self-report questionnaire. Heart disease is defined as a history of ischemic heart disease and heart failure. Subsequently, portable ultrasonographic devices were carried to the temporary housing gathering places. Technologists with ≥ 10 years of experience in performing lower extremity venous ultrasound examinations and clinical vascular technologists certified by the Japan Register of Clinical Vascular Technologists (including Japanese Society for Vascular Surgery, Japanese College of Angiology, Japanese Society of Phlebology and Japan Atherosclerosis Society) were responsible for ultrasonographic examinations, which were performed by more than one technologists. To improve consistency, the evaluation criteria were discussed before the examinations. Screening was performed with portable sonography machines using a 7.5-MHz linear probe (LOGIQ e; GE Healthcare Japan, Tokyo, Japan), a 7.5-MHz linear probe (SonoSite NanoMaxx; FUJIFILM, Tokyo, Japan), a 7.5-MHz linear probe (SonoSite TITAN; FUJIFILM), or a 3- to 12-MHz linear probe (CX50; Philips Medical Systems, Tokyo, Japan). Autopsy studies suggest that the soleal vein is the primary source of > 90% of fatal PE.[12] Untreated DVT of the calf has been reported to extend proximally and cause PE in 15% of cases.[13,14] Guidelines from the American College of Chest Physicians recommend 3 months of anticoagulation for patients with isolated DVT of the calf who are severely symptomatic or who have risk factors for proximal venous extension (e.g., patients with a history of VTE).[15] In view of the above, we focused on screening patients who were at risk of fatal PE and performed vein screening of the calf. During the ultrasonographic examination, we examined veins in the lower extremities distal to the popliteal vein, mainly the soleal veins, unless there were symptoms in the thigh because privacy cannot be maintained in the open space examination. The presence or absence of thrombi was determined based on the "Criteria for Ultrasound Diagnosis of DVT of the Lower Extremities," which is recommended by the Terminology and Diagnostic Criteria Committee of the Japan Society of Ultrasonics in Medicine.[16] The examination was performed in the sitting position, and bilateral leg veins were systematically observed. The presence or absence of thrombi was determined based on the B-mode ultrasonographic images. The presence or absence of DVT and its properties were determined using the compression and the color Doppler method. Moreover, we determined the presence or absence of soleal vein dilatation. In the present screening, we defined dilatation as a venous diameter of 9 mm or greater, as this was defined as a risk in the guidelines for DVT or PE diagnosis and treatment for residents in areas affected by the Niigata Chuetsu Earthquake.[17] On the basis of the interviews and ultrasonographic results, we retrospectively investigated the factors contributing to FCMVT in the group of patients with FCMVT and characteristic ultrasonographic findings of FCMVT.

2.3. Definition of ultrasonographic images of FCMVT

FCMVT is defined as a condition in which all of the following three ultrasonographic findings are observed: (1) thrombi filling the lumen, (2) thrombi with mixed echogenicity in parts incompletely compressed using the compression method, and (3) accompanying cordlike thrombi (bands and webs)[18] with equal-to-high echogenicity or calcification or punctate thrombi in the center of thrombi with low echogenicity and in the vessel wall. We named this characteristic ultrasound image the "blowfish sign," because of its body shape characteristics and various patterns, as a blowfish swells when threatening (Figure 1).

A mosaic pattern with a mixture of high and low echogenicity observed when thrombi are organized was excluded from FCMVT. We also distinguished the characteristic findings of acute-phase thrombi, chronic-phase thrombi, and FCMVT based on the effects of the compression method. Acute-phase thrombi are deformed by the compression method but become incomplete noncompressed parts and develop low internal echogenicity homogeneously. Chronic-phase thrombi contain calcified and cordlike thrombi, resulting in incomplete noncompressed parts. FCMVT causes incomplete noncompressed parts in which calcified thrombi, cordlike thrombi, and filling thrombi with low echogenicity are mixed. Based on the above definitions, we retrospectively examined the ultrasonographic findings of FCMVT according to the internal B-mode findings in thrombi and the change in echogenicity inside thrombi during compression and noncompression using the compression method.

2.4. Statistical analysis

Age and the diameter of the soleal vein are reported as means ±

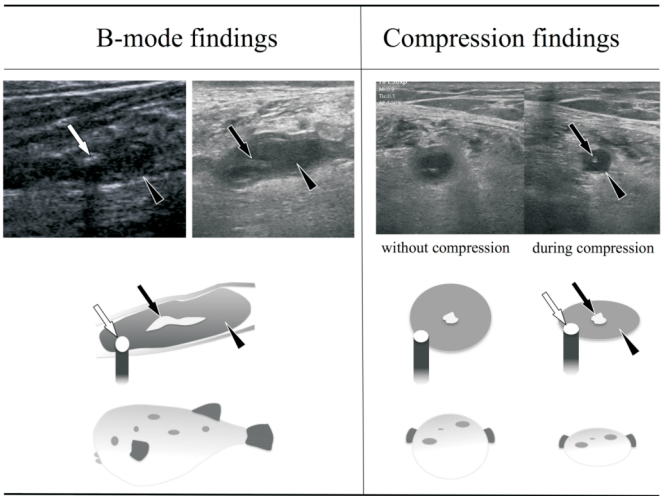

Figure 1. Image and schema of "the blowfish sign." Calcified thrombi (white arrow). Cordlike thrombi (black arrow). Fresh thrombi filling the lumen (black arrowhead).

standard deviations, and categorical variables are reported as frequency and percentage (%). Statistical analysis was performed using R commander version 1.42, and Fisher's exact test and Mann-Whitney U test were used to compare the two groups. To compare the three groups, Fisher's exact test (for multiple comparisons of two groups, Bonferroni's test) and Kruskal-Wallis test (for multiple comparisons of two groups, post hoc tests, and the Steel-Dwass multiple comparison) were used.

To identify factors contributing to FCMVT, we performed multivariate logistic regression analysis (stepwise method). For all comparisons, p values < 0.05 were considered statistically significant.

This study was approved by the University of Fukui Medical Ethics Review Committee (20160024 and 20160089) and was performed in accordance with the ethical standards of the Declaration of Helsinki.

3. Results

3.1. Detection rate of thrombi and their locations

Ultrasonography of the calf vein was performed on 791 individuals in all gathering places, and 113 DVT lesions were found in 93 individuals (93/791, 11.8%). Among them, 13 lesions in 11 individuals (11/791, 1.4%) were FCMVT. All 13 FCMVT lesions were detected in the soleal vein (100%).

3.2. Background of the subjects

Patients in the FCMVT group, when compared with those in the thrombus-negative group, were significantly older (81.3 ± 8.6 years vs. 71.8 ± 8.5 years, p = 0.003) and more likely to have a history of knee osteoarthritis (36.4% vs. 4.2%, p = 0.003). Similarly, compared with patients in the DVT group, patients in the FCMVT group were significantly older (81.3 ± 8.6 years vs. 73.4 ± 9.2 years, p = 0.025) and more likely to have a history of knee osteoarthritis (36.4% vs. 4.3%, p = 0.012) (Table 1).

3.3. Comparison of groups with and without FCMVT

The FCMVT group was significantly older (81.3 ± 8.6 years vs. 72.0 ± 8.6 years, p = 0.001) and more likely to have a history of knee osteoarthritis (36.4% vs. 4.2%, p = 0.001) than the group without FCMVT (Table 2).

3.4. Factors associated with FCMVT

We determined that age (odds ratio = 1.12, p = 0.001) and a history of knee osteoarthritis (odds ratio 10.4, p = 0.001) were independent contributing factors for FCMVT (Table 3).

3.5. Ultrasonographic findings of FCMVT

As shown in Figure 1, there was a mixture of filled thrombi with low echogenicity and calcified thrombi or thrombi with equal echogenicity.

3.5.1. Findings related to echogenicity when compressed using the compression method

We found 13 lesions with thrombi with mixed echogenicity in parts incompletely compressed using the compression method (100%).

4. Discussion

4.1. Factors contributing to FCMVT

Due to the cross-sectional design of this study, it is impossible to infer causality. However, the results did suggest that age and osteoarthritis of the knee are related to FCMVT.

In Japan, knee osteoarthritis is an orthopedic disease unique to elderly individuals. The incidence of DVT in patients with knee osteoarthritis increases with age, and age was found to be an independent risk factor for becoming DVT positive (odds ratio 1.075).[19] It has

Table 1
Participants' background characteristics.

	Total n = 791	Normal n = 687 (86.9)	DVT n = 93 (11.8)	FCMVT n = 11 (1.39)	*p*-value
Age (years)	72.1 ± 8.6	71.8 ± 8.5	73.4 ± 9.2	81.3 ± 8.6	0.001[a]
Sex (male/female)	200/591	180/507	18/75	2/9	0.323
Use of sleeping pills, n (%)	266 (33.6)	223 (32.5)	40 (43.0)	3 (27.3)	0.124
Smoker, n (%)	63 (8.0)	56 (8.2)	5 (5.4)	2 (18.2)	0.198
Drinking, n (%)	172 (21.7)	152 (22.1)	19 (20.4)	1 (9.1)	0.650
Heart disease, n (%)	205 (25.9)	173 (25.2)	28 (30.1)	4 (36.4)	0.370
Diabetes mellitus, n (%)	111 (14.0)	104 (15.1)	6 (6.5)	2 (18.2)	0.041[b]
Hypertension, n (%)	429 (54.2)	373 (54.3)	49 (52.7)	7 (63.6)	0.812
Dyslipidemia, n (%)	321 (40.6)	270 (39.3)	49 (52.7)	2 (18.2)	0.015[c]
Malignant tumor	37 (4.7)	31 (4.5)	6 (6.5)	0	0.666
Knee osteoarthritis	37 (4.7)	29 (4.2)	4 (4.3)	4 (36.4)	0.002[d]
Ultrasonography findings					
Soleal vein dilatation (≥ 9 mm)	124 (15.7)	98 (14.3)	25 (26.9)	1 (9.1)	0.009[e]
Maximum diameter of the soleal vein (mm)	7.1 ± 1.9	7.0 ± 1.8	7.8 ± 2.3	6.8 ± 1.8	0.001[f]

Mean ± standard deviation, Number of cases (% or Unit).

DVT: deep venous thrombosis; FCMVT: fresh and chronic mixed venous thrombosis; Kruskal–Wallis test (multiple comparisons of two groups at a time with post hoc adjustment and Steel–Dwass multiple comparisons).

Fisher's exact test (multiple comparisons of two groups at a time with Bonferroni adjustment).

[a] FCMVT vs. DVT (0.025), FCMVT vs. Normal (0.003), DVT vs. Normal (0.192). [b] FCMVT vs. DVT (0.600), FCMVT vs. Normal (1.000), DVT vs. Normal (0.075).

[c] FCMVT vs. DVT (0.157), FCMVT vs. Normal (0.650), DVT vs. Normal (0.054). [d] FCMVT vs. DVT (0.012), FCMVT vs. Normal (0.003), DVT vs. Normal (1.000).

[e] FCMVT vs. DVT (0.852), FCMVT vs. Normal (1.000), DVT vs. Normal (0.011). [f] FCMVT vs. DVT (0.335), FCMVT vs. Normal (0.996), DVT vs. Normal (0.001).

Table 2
Comparison of background characteristics between groups with and without FCMVT.

	Without FCMVT (DVT and Normal) n = 780 (98.7)	FCMVT n = 11 (1.39)	*p*-value
Age (years)	72.0 ± 8.6	81.3 ± 8.6	0.001
Sex (male/female)	198/582	2/9	0.739
Use of sleeping pills, n (%)	263 (33.7)	3 (27.3)	0.759
Smoker, n (%)	61 (7.8)	2 (18.2)	0.216
Drinking, n (%)	171 (21.9)	1 (9.1)	0.472
Heart disease, n (%)	201 (25.8)	4 (36.4)	0.488
Diabetes mellitus, n (%)	110 (14.1)	2 (18.2)	0.661
Hypertension, n (%)	422 (54.1)	7 (63.6)	0.762
Dyslipidemia, n (%)	319 (40.9)	2 (18.2)	0.215
Malignant tumor	37 (4.7)	0	1
Knee osteoarthritis	33 (4.2)	4 (36.4)	0.001
Ultrasonography findings			
Soleal vein dilatation (≥ 9 mm)	123 (15.8)	1 (9.1)	1
Maximum diameter of the soleal vein (mm)	7.1 ± 1.9	6.8 ± 1.8	0.803

Mean ± standard deviation, Number of cases (% or Unit).
DVT: deep venous thrombosis; FCMVT: fresh and chronic mixed venous thrombosis; Continuous variables: Mann–Whitney U test, Nominal variables: Fisher test.

Table 3
Contributing factors associated with FCMVT.

	Odds ratio	95% CI (upper–lower)	*p*-value
Age (years)	1.12	1.040–1.200	0.001
Sex (male)	0.52	0.104–2.610	0.426
Knee osteoarthritis	10.4	2.750–39.400	0.001

Multiple logistic regression analysis (binomial logistic regression analysis).
CI: confidence interval, FCMVT: fresh and chronic mixed venous thrombosis.

been reported that among patients with a history of VTE, 3.4% experienced a recurrence of venous thrombosis 3 months undergoing surgery for osteoarthritis.[20] In the present investigation, FCMVT was found to occur significantly more frequently in disaster victims who were older and had a history of knee osteoarthritis. It is presumed that the mobility of elderly disaster victims with knee osteoarthritis is more restricted than that of young people, which causes blood stagnation and triggers thrombus formation. Moreover, it is presumed that decreased blood flow around the remaining thrombi induces the development of fresh thrombi around the remaining thrombi, with the remaining thrombi being nuclei, resulting in the formation of FCMVT. We suggest that in elderly disaster victims with knee osteoarthritis, continuing blood stagnation due to decreased mobility and blood stagnation due to remaining thrombi contributed to the occurrence of FCMVT.

4.2. Ultrasonographic images and mechanisms of FCMVT

With regard to the ultrasonographic properties of thrombi, the disease stage can be estimated to some degree based on echogenicity, compressibility, hardness, regression, and the degree of recanalization, with these characteristics varying between the acute, subacute, and chronic phases.[21] Previous studies have suggested that echogenicity inside thrombi visualized by B-mode ultrasonography increases over time and is correlated with histological characterics.[22] In the present study, the ultrasonographic images of FCMVT showed thrombi with equal echogenicity or calcified thrombi with high echogenicity mixture to filling thrombi with low echogenicity. We believe these are mixed ultrasonographic images of fresh thrombi and chronic thrombi. We consider that diagnostic accuracy based on the properties of thrombi increases with the aggressive use of the compression method and by checking whether the thrombi have mixed echogenicity internally by compression. Hence, we believe that FCMVT involves a mixture of fresh thrombi and organized thrombi, which are components of the blowfish sign.

FCMVT was localized in the soleal vein of the lower leg in all cases. It is known that the soleal vein is frequently the initial site of DVT in the lower leg.[23] It is said that although many of thrombi that developed in the soleal vein disappear by fibrinolysis after a few days or weeks, some remain as localized organized thrombi, and approximately 20% extend toward the center.[24] Because veins in which thrombi formed have damaged vascular endothelia, they become hotbeds of fresh thrombi, with the remaining organized thrombi acting as nuclei, and the sudden increase of thrombi leads to sudden death due to PE.[11] We presume that, among the cases that we encountered in this investigation, blood stagnation by the remaining thrombi after thrombus formation acted as a risk factor for the development of FCMVT. We presume that the stenosis of the soleal vein by the remaining thrombi decreases the blood flow around the thrombi and changes the venous diameter, which results in turbulent flow and facilitates the development of secondary thrombi around the remaining thrombus. If thrombi form again around the old organized thrombi in the veins in the lower leg, it is presumed that a chain of recurrence and organization of thrombi could be repeated because of continuing blood stagnation caused by the organized thrombi. To break this chain, it is important to prevent DVT formation, which is the initial lesion, and to leave behind no organized thrombus after treatment. In the present study, we were unable to identify a causal relationship between FCMVT showing the blowfish sign and PE. However, taking into consideration the fact that fatal PE was mostly observed in the soleus vein and that fresh and organized thrombi were mixed in the vein,[11,12] we speculate that FCMVT showing the blowfish sign may be a risk thrombus for PE. Thus, to prevent PE, it is important to detect high-risk thrombi via the early identification of changes in thrombus characteristics. In particular, the blowfish sign is likely to be suggestive of FCMVT, and its detection by ultrasonography is very important for preventing PE. In the elderly, in patients with a history of KOA, and in patients with residual thrombus, there is a risk of causing FCMVT. Untreated DVT of the calf has been reported to extend proximally and cause PE in 15% of the cases.[13,14] Continuous monitoring and follow-up of susceptible disaster victims is necessary to prevent the development of FCMVT in these patients. In addition to exercise, drinking water, and undergo-

ing regular ultrasonographic examinations, it is necessary to improve the environment of the shelter to prevent thrombosis. Moreover, it is important to encourage individuals to practice both lower limb and ankle exercise together to prevent venous thrombosis, but as in the case of the coronavirus disease-2019 pandemic, evacuation during infectious disease epidemics is based on decentralized evacuation. Therefore, it is necessary to establish remote exercise therapy with the technology of the Internet of Things. Implementation of preventive measures is expected to prevent PE that may occur in the future. Prospective interventions should be provided for disaster victims until they can return to their normal lives.

4.3. Limitations

This study has some limitations. First, as screening was conducted by a volunteer-based team within a limited timeframe, not all disaster victims in temporary housing were assessed. Second, the number of FCMVT cases was small, making the size of the groups uneven. As our study area was a part of the disaster area, the estimated thrombosis prevalence in the sample can be generalized to older people in the disaster area. Third, the diagnosis was made using only ultrasonography. Because the internal echo of venous thrombi varies, diagnosis based on the echogenicity of thrombi needs to be made carefully. Fourth, because medical history and lifestyle habits were self-reported during the interview, the actual influences cannot be analyzed. Hence, future studies should consider these issues.

5. Conclusion

Compared with patients in the DVT and thrombus-negative groups, participants in the FCMVT group tended to be middle-aged or elderly and have a higher prevalence of knee osteoarthritis. FCMVT of the calf showed a characteristic finding, namely the blowfish sign, which represents a mixture of thrombi with low echogenicity, equal echogenicity, and calcification. Long-term prevention and the establishment of a support system for patients with FCMVT are needed.

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Conflicts of interest

All authors have no conflicts of interest to declare.

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