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Self-reported symptoms and risk factors for digital ischaemia among international world-class beach volleyball players

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ABSTRACT

The prevalence of ischaemia-related symptoms is remarkably high among elite indoor volleyball players. Since the exposure to sport-specific demands may be higher in beach volleyball compared to indoor volleyball, the aim of this study was to assess the prevalence of ischaemia-related symptoms and associated risk factors among world-class beach volleyball players. Therefore, a questionnaire survey was performed among beach volleyball players active during the 2013 Grand Slam Beach Volleyball in the Netherlands. In total, 60 of the 128 beach volleyball players (47%) participated: 26 males and 34 females from 17 countries. The self-reported prevalence of cold or blue or pale digits in the dominant hand during or immediately after practice or competition was 38% ($n = 23$). Two risk factors were independently associated with symptoms of blue or pale digits: more than 14 years playing volleyball (odds ratio (OR) 4.42, 90% confidence interval (90% CI) 1.30–15.07) and sex (female) (OR 4.62, 90% CI 1.15–18.57). In conclusion, the prevalence of symptoms associated with digital ischaemia is high among international world-class beach volleyball players. Female sex and the length of the volleyball career were independently associated with an increased risk of ischaemia-related symptoms. The high prevalence of these seemingly innocuous symptoms and possible associated risk factors warrant regular monitoring since early detection can potentially prevent thromboembolic complications and irreversible tissue damage.

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KEYWORDS

Beach volleyball; finger/hand ischaemia; prevalence; risk factors; arterial pathology

Introduction

In the medical literature, cold and discoloured digits were reported by 89% of volleyball players with confirmed digital ischaemia caused by emboli due to pathological changes of the posterior circumflex humeral artery (PCHA) in the ipsilateral shoulder (Figures 1 and 2) (Van De Pol, Kuijer, Langenhorst, & Maas, 2012). These data, although self-reported, strongly suggest underlying PCHA pathology; however, this exact association has yet to be confirmed. Distal embolisation from an aneurysmal and thrombosed PCHA can disable the athlete and threaten the athlete's career and viability of the involved parts. Invasive treatment possibilities involve surgical ligation and endovascular coiling (Atema, Ünlü, Reekers, & Idu, 2012), while conservative treatment consists of cessation of sports activities. Active surveillance might make it possible to identify vascular injury at an early stage in those volleyball players who experience apparently innocuous symptoms. This way, thromboembolic complications and irreversible tissue damage can potentially be prevented.

Volleyball is unique among team sports in that it has evolved into two distinct Olympic disciplines: a two-person per side outdoor game typically played on sand (beach volleyball) and an indoor version featuring six players on each team (indoor volleyball). The Fédération Internationale de Volleyball (FIVB) estimates

that 500 million people play volleyball worldwide, with the greatest area of growth in beach volleyball (Reeser, 2008). Although the essential skills of the two disciplines are identical, beach volleyball distinguishes itself from indoor volleyball through several characteristics, the most obvious being the composition of the playing surface.

Game-specific characteristics might lead to different demands placed on the upper extremity. For instance, higher rates of overuse injuries of the shoulder have been reported in beach volleyball compared to indoor volleyball (Aagaard, Scavenius, & Jørgensen, 1997). In this regard, among elite male indoor volleyball players in the Netherlands, one-third reported symptoms of cold, blue and/or pale digits in the dominant hand during volleyball, with the length of the volleyball career and the intensity of performing strength-increasing weight training identified as associated risk factors (Van De Pol, Kuijer, Langenhorst, & Maas, 2014).

These high rates of symptoms related to digital ischaemia among young and fit elite male indoor volleyball players stress the need for an inventory of these numbers in elite beach volleyball players. Therefore, the aim of this study was to assess the prevalence of known ischaemia-related symptoms and associated risk factors among international world-class beach volleyball players.

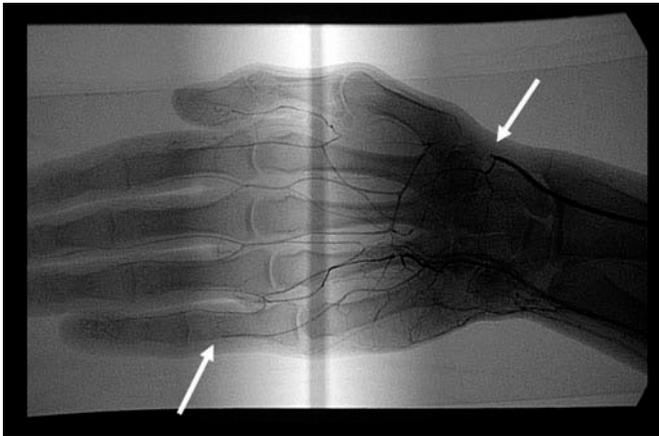


Figure 1. Digital subtraction angiography of the right hand of a 27-year-old volleyball player with ischaemic symptoms of multiple digits. The arrows point to multiple abrupt stops in digital arteries, compatible with microemboli (Van De Pol et al., 2012).



Figure 2. Digital subtraction angiography of the right arm of a 27-year-old volleyball player with ischaemic symptoms of multiple digits (the same player as in Figure 1). The arrow points to the abrupt stop of contrast in the posterior circumflex humeral artery caused by thrombosis (Van De Pol et al., 2012).

Materials and methods

Study design

A cross-sectional questionnaire survey was performed among international world-class beach volleyball players during the 2013 Beach Volleyball Grand Slam Tournament in the Hague, the Netherlands. Official approval for the study was granted by the Medical Ethics Review Committee, and permission was obtained from the medical commission at the FIVB.

Participants

After permission was granted by the FIVB and the Dutch Volleyball Association (Nevobo), all players, coaches and medical staff were informed about the study via email and during the technical meeting that all teams were required to attend. Athletes were invited to participate at any time during the tournament and were actively asked during the tournament by the main researcher and volunteers. During the 4-day main tournament, the athletes were surveyed onsite in the medical treatment area.

The main tournament of the Beach Volleyball Grand Slam Tournament consisted of 32 male teams and 32 female teams, which resulted in 128 potential participants. To obtain a large study sample, both male and female athletes were invited. Written informed consent was obtained. The inclusion criteria were (1) full competitive activity during the main tournament and (2) written informed consent. Exclusion criteria included a history of vascular injury or surgery of the dominant shoulder, confirmed Raynaud's phenomenon, use of cardiovascular medication and age below 18 years.

Questionnaire content

A specifically developed questionnaire to detect ischaemic symptoms and to identify known risk factors associated with digital ischaemia in volleyball was used. This questionnaire was developed by Van de Pol et al. using reports of volleyball players with confirmed digital ischaemia and based on evidence from the medical literature, and was also used among professional indoor volleyball players (online supplementary Appendix A) (Van De Pol et al., 2012, 2014). The questionnaire comprised four general domains: (1) those regarding demographics, such as age; (2) those regarding personal risk factors and medical conditions, such as family history of cardiovascular disease; (3) those regarding known sports-related risk factors, such as years spent playing volleyball; and (4) those regarding specific symptoms associated with digital ischaemia, such as cold digits during practice or competition.

Data analyses

Data were entered in SPSS (version 20.0, SPSS Inc, Chicago, IL, USA) and correct data entry was checked for by a second researcher.

Characteristics of the participants

The mean, standard deviation, minimum and maximum of respectively age, body height, body weight, total years playing volleyball, total years playing beach volleyball, total years playing professional volleyball and weekly hours playing volleyball in practice or competition were reported for the total group of beach volleyball players, and for males and female separately. Additionally, the percentage of beach volleyball players that reported a family history of cardiovascular disease and smoking were reported.

Prevalence of symptoms

The prevalence of symptoms associated with digital ischaemia was calculated in the following manner: the percentage of all

beach volleyball players who sometimes or more often reported having cold or blue or pale digits in the dominant hand during or directly after practice or competition. These prevalences were reported for the total group of beach volleyball players, and for males and females separately.

Then, participants were stratified according to a positive history of the two more severe ischaemia-related symptoms reported in the questionnaire, namely blue or pale. The case definition of the symptomatic group was "reporting symptoms of blue or pale digits in the dominant hand during or immediately after practice or competition". The reference group was defined as players without these two symptoms.

Risk factors

First, to assess differences between the symptomatic and reference group, demographical parameters, and personal and sports-related risk factors were tested using an independent *t*-test or a χ^2 test (online supplementary Appendix B). In all tests, a *P*-value ≤ 0.10 was considered significant. This cut-off value was deliberately chosen since this is the first study on these symptoms among international beach volleyball players and, given the relatively small group size, a *P*-value of ≤ 0.10 is warranted to overcome missing potential clinically relevant differences.

Next, the odds ratio (OR) and 90% confidence interval (90% CI) were calculated for all demographical, personal and sports-related risk factors using a univariate binary logistic regression. Subsequently, the collinearity between the univariately analysed variables with a *P*-value ≤ 0.10 was calculated. For all non-collinear variables with a *P*-value < 0.10 , an OR including 90% CI was calculated using a multivariate binary logistic regression, and subcategory analyses will be performed in line with Van De Pol et al. (2014).

Results

Participants

In total, 63 of the 128 eligible beach volleyball players (64 males and 64 females) voluntarily participated in the study (49%). Three players (two males and one female) were excluded from the study due to confirmed Raynaud's phenomenon. As a result, 60 beach volleyball players from 17 countries, 26 males and 34 females, were included in our study, an inclusion rate of 47%.

On average, participants were 26 years old, had a body height of 186 cm and had been playing beach volleyball for 13 years and 19 h a week (Table 1). Twenty-three per cent of the participants reported the presence of cardiovascular

disease in their family. Eighteen per cent smoked or had smoked in the past. Male beach volleyball players were on average 27 years old, had a body height of 1.95 m and had a volleyball career length of 14 years (Table 1). Female beach volleyball players were on average 26 years old, had a body height of 1.79 m and had a volleyball career length of 13 years (Table 1). Among the male participants, 27% (*n* = 7) reported that they smoked or had smoked in the past, while among the female participants this figure was 12% (*n* = 4).

Prevalence of symptoms associated with digital ischaemia in the dominant hand

The prevalence of symptoms of pale digits during practice or competition in the participants was 18% (Table 2). Ten per cent reported pale digits after practice or competition. The prevalence of participants that reported the combination of blue or pale digits in the dominant hand during or immediately after practice or competition was 22%.

Factors associated with complaints of ischaemic symptoms

The symptomatic group of players who reported "blue or pale digits in the dominant hand during or directly after practice or competition sometimes or more often" consisted of 13 beach volleyball players. The reference group consisted of 47 beach volleyball players.

Demographical parameters

The symptomatic group consisted of 2 males and 11 females, and the reference group of 24 males and 23 females – a significant difference ($\chi^2 = 5.30$, *P* = 0.02) (online supplementary Appendix B). The independent *t*-test revealed no significant differences between the groups for other demographical

Table 2. Prevalence of self-reported symptoms (or combinations thereof) associated with digital ischaemia during or immediately after practice or competition in the dominant hand in international world-class beach volleyball players.

	Total group <i>n</i> = 60		Male <i>n</i> = 26		Female <i>n</i> = 34	
Cold digits during	15	25%	5	19%	10	29%
Cold digits after	10	17%	3	12%	7	21%
Blue digits during	2	3%	1	3%	1	3%
Blue digits after	2	3%	0	0%	2	6%
Pale digits during	11	18%	2	8%	9	27%
Pale digits after	6	10%	0	0%	6	18%
Blue or pale digits, during or after	13	22%	2	8%	11	32%
Cold or blue or pale digits, during or after	23	38%	6	23%	17	50%

Table 1. Characteristics of the participants.

	Total					Male					Female				
	<i>N</i>	Mean	SD	Min	Max	<i>N</i>	Mean	SD	Min	Max	<i>N</i>	Mean	SD	Min	Max
Age (years)	60	26.1	3.6	18	36	26	26.7	4.1	18	36	34	25.8	3.1	21	35
Body height (cm)	60	186	10.1	170	212	26	195	7.8	179	212	34	179	4.9	170	191
Body weight (kg)	60	77.6	12.4	59	107	26	89.1	8.9	63	107	34	68.8	5.5	59	83
Total years volleyball	59	13.3	4.7	4	29	25	13.5	5.6	4	29	34	13.1	4.0	6	21
Years beach volleyball	57	9.0	3.5	2	18	24	10.2	3.8	2	18	33	8.2	3.0	4	14
Years professional volleyball	59	6.0	2.8	1	13	26	6.2	2.9	1	13	33	5.9	2.7	2	13
Hours volleyball per week	59	19.4	6.4	4	40	26	19.4	6.2	4	30	33	19.5	6.7	8	40

Table 3. Univariate binary logistic regression outcomes (odds ratio and 90% confidence interval) of demographics and potential risk factors associated with self-reported symptoms of digital ischaemia in international world-class beach volleyball players.

	Symptomatic group versus reference group
<i>Domain A: demographics</i>	
Age	OR 1.09 (90% CI 0.94–1.26)
Sex (female)	OR 5.75 (90% CI 1.48–22.22) *
Height	OR 0.98 (90% CI 0.933–1.04)
Weight	OR 0.96 (90% CI 0.91–1.01)
<i>Domain B: personal risk factors</i>	
Raynaud in family (yes)	OR 0.00 (90% CI 0.00–) **
Family history on cardiovascular disease (yes)	OR 2.64 (90% CI 0.86–8.08)
Smoking (yes)	OR 0.31 (90% CI 0.05–1.88)
<i>Domain C: sports-related risk factors</i>	
Total years playing volleyball	OR 1.12 (90% CI 1.00–1.25) *
Years playing beach volleyball	OR 0.97 (90% CI 0.82–1.14)
Years playing professional volleyball	OR 1.01 (90% CI 0.84–1.22)
Total practice and competition hours in a week	OR 1.00 (90% CI 0.92–1.09)
Smashing/spiking frequency	OR 4.41 (90% CI 0.76–25.62)
Smashing/spiking “away from the shoulder” (often/always)	OR 1.06 (90% CI 0.35–3.21)
Performing dominant limb weight training in general (yes)	OR 2.79 (90% CI 0.23–34.18)
Frequency of performing weight training to increase dominant limb strength (often/always)	OR 0.75 (90% CI 0.26–2.19)
Number of hours per week performing weight training to increase dominant limb strength	OR 1.08 (90% CI 0.56–2.08)
Frequency of performing weight training to maintain dominant limb strength (often/always)	OR 3.24 (90% CI 0.53–19.81)
Number of hours per week performing weight training to maintain dominant limb strength	OR 74.31 (90% CI 0.00–1.15E)

Notes: * Significant ($P \leq 0.10$).

**No odds ratio (OR) could be calculated as no volleyball players reported being exposed to this risk factor.

parameters like age and body height (online supplementary Appendix B).

The univariate binary logistic regression also revealed a significant association for the demographical parameter sex (OR 5.75, 90% CI 1.48–22.22) (Table 3).

Personal risk factors

Thirty-nine per cent of the beach volleyball players in the symptomatic group reported the presence of cardiovascular disease in their family, while in the reference group this was 19%. Eight per cent of the beach volleyball players in the symptomatic group reported that they smoked or had smoked in the past. For the male players, 0% (0/2) of the symptomatic group smoked and 29% (7/24) of the reference group. For the females, these data were 9% (1/11) and 13% (3/23), respectively. The χ^2 test revealed no significant differences between the groups for all personal risk factors (online supplementary Appendix B). Additionally, no significant associations were found in the results of the univariate binary logistic regression analyses (Table 3).

Sports-related risk factors

On average, beach volleyball players in the symptomatic group had a volleyball career length of 15 years and in the

Table 4. Multivariate binary logistic regression outcomes (odds ratio and 90% confidence interval) of sex and total years playing volleyball.

Symptomatic group versus reference group	
Sex (female)	OR 4.62 (90% CI 1.15–18.57)
Total years playing volleyball	OR 1.11 (90% CI 1.01–1.21)
0–13 years ($n = 31$)	Reference
14–30 years ($n = 28$)	OR 4.42 (90% CI 1.30–15.07)

reference group 13 years – a significant difference ($t = -1.71$, $P = 0.09$). For the other sports-related risk factors, neither group differed significantly (online supplementary Appendix B).

The univariate binary logistic regression also revealed a significant association for total years playing volleyball (OR 1.12, 90% CI 1.00–1.25). For the other sports-related factors, the univariate binary logistic regression revealed no significant associations like total practice and competition hours in a week (OR 1.00, 90% CI 0.92–1.09) or the frequency of performing weight training to increase dominant limb strength (OR 0.75, 90% CI 0.26–2.19) (Table 3).

Multivariate regression outcomes

No collinearity between sex and total years playing volleyball was found (variance inflation factor = 1.004, tolerance = 0.996). The multivariate binary logistic regression revealed a significant association for sex (female) with an OR 4.62 (90% CI 1.15–18.57) (Table 4). Total years playing volleyball categorised in two categories (0–13 years and 14–30 years) showed a significant association for the subcategory 14–30 years playing volleyball with OR 4.42 (90% CI 1.30–15.07) (Table 4).

Discussion

The two main findings are (1) the prevalence of participants reporting blue or pale digits in the dominant hand during or immediately practice or competition was 22% ($n = 13$) and (2) volleyball career length and sex were independently associated with an increased risk on ischaemia-related symptoms of the dominant hand.

Prevalence: difference between elite male beach volleyball players and elite male indoor volleyball players

This is the first study that reports the prevalence of symptoms associated with digital ischaemia in international world-class beach volleyball players. The reported prevalence of blue or pale digits during practice or competition in the dominant hand among the participating elite male beach volleyball players ($n = 24$) was lower than the reported prevalence among elite male indoor volleyball players in the Netherlands ($n = 99$) (8% vs. 26%, respectively) (Van De Pol et al., 2012). This difference was significant (OR 0.23, 90% CI 0.04–0.93, $P = 0.06$) This result seems to invalidate the hypothesis that beach volleyball players are more prone to ischaemia-related symptoms of the dominant hand, and possibly putative sport-specific vascular injuries of the dominant limb, than indoor volleyball players. This lower prevalence might be related to game-

specific differences between beach and indoor volleyball. First, beach volleyball players are shorter in height and weigh less compared to indoor volleyball players (Palao, Gutiérrez, & Frideres, 2008). This might be related to different biomechanical, physiological, and tactical and technical demands. Biomechanical differences in beach volleyball compared to indoor volleyball are those related to the adaptation, for instance, the kinematics of the approach phase, or the movement of the centre of mass due to playing in the sand. However, recently no differences have been reported for upper limb amplitude of motion or angular velocity (Tilp, Wagner, & Müller, 2008). An example of a physiological difference is the greater area that beach volleyball players have to cover: two players covering an 8 × 8 m field compared to a 9 × 9 m with six players in indoor volleyball. Lastly, and closely related to the preceding, tactical and technical strategies are that off-speed placement shots to catch the opponent off guard, like tips and roll shots, are a more effective game-winning strategy than the hard smashes or spikes as in indoor volleyball. This may result in less blunt trauma to the hand and digits, and less fierce repetitive rotary movements in the shoulder of beach volleyball players. Other possible preventive elements in beach compared to indoor volleyball are the reduced air pressure in the beach volleyball (0.175–0.225 kg · cm⁻² vs. 0.300–0.325 kg · cm⁻²), and the considerably lower average duration of a beach volleyball match (50 min with 90 rallies vs. 95 min with 165 rallies) (José Manuel Palao, Valades, & Ortega, 2012). In addition, Raynaud-like symptoms, like pale digits, are known to be aggravated by cold circumstances (Block & Sequeira, 2001; Wigley, 2002) and might therefore be less provoked in the warm seasons and environmental temperatures in which beach volleyball is generally played.

Sports-related risk factor for symptoms associated with digital ischaemia

This is the first study to identify a sports-related risk factor for symptoms associated with digital ischaemia among beach volleyball players. A significant fourfold increased risk was found for a volleyball career length of more than 14 years volleyball, and the increased risk per played volleyball year was 1.11. The influence of the volleyball career length on symptoms of digital ischaemia in elite volleyball was also established in elite male indoor volleyball players in the Netherlands with a similar significant 1.1-fold (95% CI 1.01–1.21) increased risk per played volleyball year.

A possible explanation for the risk factor volleyball career length might be that the exposure to blunt trauma to the forearms and hands, and repetitive rotary movements of the shoulder, increase gradually during a volleyball player's career, resulting in a deterioration of vascular structures (Van De Pol et al., 2014). For example, a highly skilled indoor volleyball attacker with 16–20 h weekly practice time performs about 40,000 smashes/spikes in a single season (Kugler, Krüger-Franke, Reiningger, Trouillier, & Rosemeyer, 1996). Despite the fact that no comparable numbers were found for beach volleyball, this figure

might well be indicative for high-level beach volleyball players. This cumulative sport-specific exposure might well have contributed to proven cases of ischaemia-related symptoms of the hand in volleyball players as a result of local vascular trauma in the forearm and (hypo)thenar (Kostianen & Orava, 1983; Massada, Aido, Magalhaes, & Puga, 2011) or an overload of vascular structures in the shoulder like the PCHA (Atema et al., 2012; McIntosh, Hassan, Cherry, & Dahm, 2006; Reekers, Den Hartog, Kuyper, Kromhout, & Peeters, 1993; Reekers & Koedam, 1998; Stänz, Wedler, Köpfl, Künzi, & Pfammatter, 2001; Van De Pol et al., 2012; Vlychou, Spanomichos, Chatziioannou, Georganas, & Zavras, 2001).

Sex as a risk factor for symptoms associated with digital ischaemia

Prevalence of sex differences in health-related outcomes in beach volleyball has been reported. For example, female beach volleyball players have more injuries to the hands and fingers, and fewer injuries to the ankle/foot (Augustsson, Augustsson, Thomeé, & Svantesson, 2006; Solgård et al., 1995). Female beach volleyball players in the present study reported a higher prevalence for all symptoms (or combinations thereof) associated with digital ischaemia than their male colleagues (Table 2). These differences might be explained by sex-specific game characteristics and general sex differences. Examples of sex-specific differences in game characteristics are fewer terminal actions and more continuous actions in defence and attack in women's games (Koch & Tilp, 2009), which is likely to contribute to a longer playing time per point in women's games, thereby increasing cumulative exposure for the upper extremity.

Apart from technical and tactical differences among sex, other variables might explain the differences observed in our female population. Firstly, women are more likely to perceive cold in hands and digits due to differences in peripheral vascularisation, fat distribution, hormonal regulation, nerve distribution and sensitivity to temperature alterations (Bastiaansen, Jochems, Tervoort, & Jüngen, 2007). Secondly, women are known to have an increased risk of vasoconstriction in the hand leading to cold and pale digits, as is seen in Raynaud's phenomenon (Block & Sequeira, 2001). Thirdly, women indicate and cope with physical discomfort differently, which might explain the increased female-to-male ratio in clinical settings (Greenspan et al., 2007). Interestingly, in their study on volleyball-related shoulder pain, Reeser et al. (2010) stated that even if there were no significant sex differences in the prevalence of shoulder problems female volleyball players reported lower overall shoulder function and sought medical care more frequently than male volleyball players (Reeser et al., 2010).

Relevance for clinical sport practice

Consensus among studies in volleyball players exists about the added value of identifying symptoms and risk factors in an early stage to decrease time lost from sports participation and to develop effective preventive measurements

(Bahr, 2009; Bahr & Krosshaug, 2005; Briner & Kacmar, 1997; Reeser, Verhagen, Briner, Askeland, & Bahr, 2006). Prospective assessment of the prevalence of symptoms at regular intervals seems most suitable to identify overuse injuries (Bahr, 2009). These types of injuries are characterised by discomfort, do not necessarily cause a player to stop playing and lead to postponed detection and medical treatment (Seminati & Minetti, 2013; Verhagen, Beek, Bouter, Bahr, & Mechelen, 2004). Symptoms of digital ischaemia are suited for surveillance because they meet these criteria, including the Wilson and Jungner criteria for surveillance, like the presence of an early symptomatic stage, a suitable test and available treatment (Wilson & Jungner, 1968). The short screening questionnaire (online supplementary Appendix A) might be of use for this purpose. We recommend the frequency to be higher for beach volleyball players with a career length of more than 14 years. In the case of inducing or exacerbating of the symptoms, low threshold additional imaging, for instance, with colour Doppler ultrasound of the whole dominant upper limb, should be applied to exclude structural vascular pathology.

Strengths and limitations

The inclusion rate of 47% in this study is both a strong and a weak point. Considering that all 60 participants are young, fit and healthy athletes at the top of their sports career, the included population seems a valid cohort of world-class beach volleyball players. However, 47% merely represents half of the tournament's competitors, and selection bias might be present. It is possible that certain volleyball players, for instance, symptomatic or female athletes, were more inclined to participate. No group matching for sex was performed, simply because the goal was to include as many world-class beach volleyball players as possible. Had the other half of the volleyball players not reported any symptoms, the prevalence would still be about 19% (half of 38%, Table 2) for cold, blue or pale digits. Even in that case, regular monitoring of these seemingly innocuous symptoms seems warranted in these young, fit and healthy males and females.

Although the content validity of our questionnaire is established based on reports of volleyball players with confirmed digital ischaemia from the literature and from medical files (Van De Pol et al., 2012), upcoming studies should reveal the sensitivity and specificity of the reported ischaemic complaints for pathological changes of the PCHA in the shoulder of both elite beach and indoor volleyball players.

In conclusion, the prevalence of symptoms associated with digital ischaemia is high among international world-class beach volleyball players. Female sex and the length of the volleyball career were independently associated with an increased risk of ischaemia-related symptoms. The high prevalence of these seemingly innocuous symptoms and possible associated risk factors warrant regular monitoring since early detection can potentially prevent thromboembolic complications and irreversible tissue damage.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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