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"Worry is a thin stream of fear trickling through the mind. If encouraged, it cuts a channel into which all other thoughts are drained."

Arthur Somers Roche (1883-1935)
American writer

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Editorial

Pandemic Preparedness: Nationally-Led Simulation to Test Hospital Systems

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Introduction

Cities that receive large numbers of international travellers are particularly vulnerable to outbreaks of emerging infectious disease with pandemic potential.[1] Secondary transmission of Ebola virus disease (EVD) occurred when travellers from West Africa infected healthcare workers in Europe and the United States in 2014.[2,3] Middle East respiratory syndrome (MERS) coronavirus has also caused secondary outbreaks due to travel by infected individuals. While most of these distant outbreaks of MERS have to date been quickly confined, South Korea experienced 185 laboratory-confirmed cases involving 5 generations of transmission over 6 weeks.[4] In Singapore, the Nipah virus in 1998 to 1999, severe acute respiratory syndrome (SARS) coronavirus in 2003 and influenza A/H1N1 in 2009[5] not only had a major impact on the health of its population and notably its healthcare workers, but also more broadly, affected the economy.

EVD outbreaks have occurred regularly in Africa. They have been invariably controlled and halted using conventional infection control practises.[6] However, the 2014 to 2015 EVD outbreak was the largest and the first to leave African shores. The risk of EVD to countries outside of Africa was a concern shared by many health administrations, including those of Singapore.

There is an expectation in Singapore that each healthcare facility will be prepared for the presentation of a traveller with a novel transmissible infectious disease. The cornerstone of providing safety against an infectious disease threat is early identification of a suspect case through robust triage mechanisms at potential sites of patient presentation followed by the institution of rigorous infection prevention and control precautions. Facility-level preparation is typically undertaken by individual healthcare facilities and their key stakeholders. Table 1 shows a generic checklist of requirements for hospital preparation, encompassing in-house evaluations using "table-top" (theoretical) exercises, quality and process improvement "walkabouts", and department-specific simulation exercises.

To mitigate the threat posed by EVD, the Ministry of Health (MOH), Singapore undertook a series of "walkabouts" to assess institutional readiness in most major public and private hospitals across the country during the latter part of 2014. To further test and facilitate enhancement of systems, MOH subsequently undertook full scale national simulation exercises collectively called Exercise Sparrowhawk.

National Simulation Exercise

Prior to the exercises, hospitals were required to submit a copy of their hospital preparedness standard operating procedures to MOH for review. MOH officials and selected external infectious diseases physicians and infection control nurses formed the planning and evaluation team. Preparation commenced 3 months prior to the actual simulations. The team created a timeline for each scenario (an example is shown in Figure 1), developed a comprehensive assessment checklist and had selected MOH staff rehearse the roles of the EVD patient and relatives in respective scenarios. The checklist (Appendix 1) assessed the following domains: Response (Box 1), Personal infection control practices (Box 2), Communications (Box 3), Surveillance and epidemiology (Box 4) and Contact tracing (Box 5). The set of checklists could be adapted to assess performance at different hospital sites based on how the scenario evolved.

A series of 3 scenario-based exercises was conducted in 3 public hospitals between December 2014 and March 2015. Hospitals were informed of the exercise 3 hours prior to commencement to ensure that measures could be instituted to minimise disruption of routine healthcare. Each hospital was tested on a different date, using a different scenario.

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Table 1. Hospital Preparation for Ebola Outbreak

Domains	Requirements
Establish outbreak preparedness taskforce	Key representatives from Infectious Diseases, Infection Control, Epidemiology, Laboratory, Hospital Operations, Corporate Communications, Emergency department, Wards, Intensive Care units, outpatient clinics, operating theatres, Radiology department, Environmental Services, Security, Porters
Personal protective equipment	Protocols for donning and doffing, training of staff, availability of stock
Infrastructure and logistics	Assess capacity for: • Isolation of suspect cases in Emergency department, critical care facilities and general wards • Safe inter-hospital transfer of a patient • Safe testing of specimens • Safe environmental cleaning and waste disposal
Establishing and practising workflows	• Rapid response team led by Infection Control for urgent advice with attendance, as required • All departments that could be exposed to suspect case: Emergency, inpatient wards, outpatient clinics, Laboratory, Environmental Services, Mortuary, Communications, Epidemiology • Consider compiling workflows into a manual containing standard operating procedures
Contact tracing and surveillance system	The Epidemiology department to oversee contacts
Communications	Establish information sharing protocols prior to and after any case, involving the patient/next-of-kin, internally amongst hospital staff and externally with Ministry of Health
Human resource	Contingency plans to sustain routine healthcare
Table-top exercise	Multidisciplinary meeting to discuss and finalise workflows
Unannounced simulation exercise	• Aims to test the system and workflows, and to identify gaps • Planning of case scenarios • Assessment checklist, evaluators and exercise controllers

The first simulation exercise involved a case identified in the emergency department that required transfer to the isolation ward (Fig. 1). A second scenario involved a patient identified late in an open general ward after surgery. A third scenario involved a vomiting child who required interhospital transfer. A total of 5 exercise controllers, 3 actors and 10 evaluators facilitated each exercise. Tasks were divided between the team to ensure that an evaluator was witness to each assessment criteria.

An exercise debrief was conducted immediately at the conclusion of the scenario. This facilitated discussion that covered all aspects of the exercise performance and included the hospital staff, senior management and the evaluation team. This also included an interview and feedback from staff

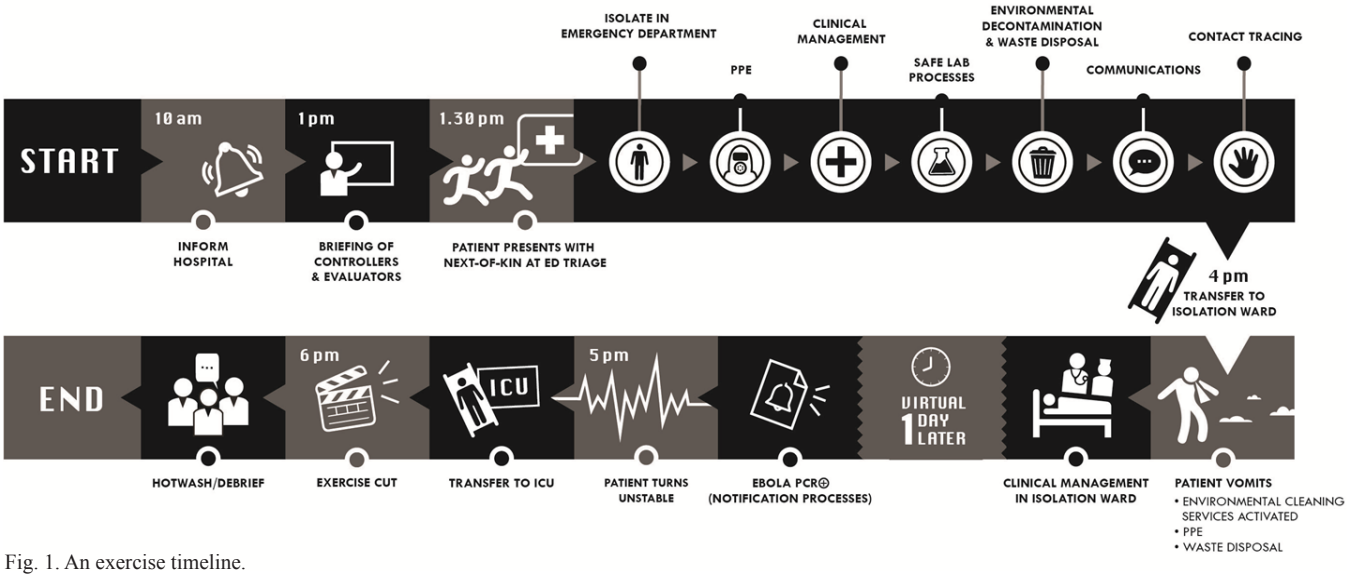

Fig. 1. An exercise timeline.

involved in the prolonged care of an EVD patient, focusing particularly on their physical and emotional well-being. The evaluation team later produced a detailed presentation on the findings and recommendations by way of feedback to hospital management as well as a written evaluation report. Hospitals were required to provide plans for rectification a month after receipt of the report.

In general, all hospitals were assessed as having robust preparedness systems to respond to a potential EVD patient. Some typical key recommendations following the exercise included:

- Scheduled ongoing training on personal protective equipment (PPE) and environmental decontamination;
- Clearer communication with the patient, next-of-kin and other healthcare workers;
- Further details for contact tracing information;
- Limiting the number of healthcare workers in contact with the suspect patient; and
- Provision of staff time limit when wearing full PPE to avoid staff exhaustion and overheating.

Conclusion

Nosocomial transmission of Ebola in Europe and the United States[2,3] highlighted the risk for secondary spread within hospitals distant from Africa even with single imported cases whose diagnosis was already known to hospital staff. Having systems and workflows in place is not sufficient. These need to be tested with gaps identified and rectified. Instituting preparedness activities such as simulation exercises is an ideal tool for this purpose.[7] Each hospital simulation required approximately 250 man-hours from the evaluation team in preparation for and undertaking of the event plus to generate the post-exercise report. Although this was moderately time-consuming and labour intensive, this increased familiarity with workflows, tested the coordination of workflows between different disciplines and allowed the identification of gaps.

It is inevitable that healthcare facilities particularly in countries well-connected globally will remain vulnerable to pandemic threats. Looking beyond the EVD outbreak, Singapore is equipped with an improved infrastructure and workflows that can be adapted for future pandemic threats. Roles and responsibilities within hospitals are clearer. The need to be prepared has facilitated a more generic awareness and state of readiness in Singapore, crystallised by a series of large scale simulation exercises.

Acknowledgement

The authors would like to thank Dariusz Olszyna, Indumathi Venkatachalam, Mo Yin, Cathrine Teo, Razali Bin Mahdi and the Communicable Diseases Division and Emergency Preparedness and Response Division, Ministry of Health, Singapore for forming the evaluation team for the simulation exercises. The authors would also like to thank Dorothy Tan for contributing to the design of Figure 1.

REFERENCES

1. Chen LH, Wilson ME. The role of the traveler in emerging infections and magnitude of travel. Med Clin North Am 2008;92:1409-32.
2. Parra JM, Salmeron OJ, Velesco M. The first case of Ebola virus disease acquired outside Africa. N Engl J Med 2014;371:2439-40.
3. Chevalier MS, Chung W, Smith J, Weil LM, Hughes SM, Joyner SN, et al. Ebola virus disease cluster in the United States- Dallas County, Texas, 2014. MMWR Morb Mortal Wkly Rep 2014;63:1087-8.
4. World Health Organization. MERS-CoV in the Republic of Korea at a glance. Available at: http://www.wpro.who.int/outbreaks_emergencies/wpro_coronavirus/en/. Accessed on 8 October 2015.
5. Goh LG. Emerging infections and role of family physician. The Singapore Family Physician 2014;40:8-10.
6. Khan AS, Tshioko FK, Heymann DL, Gueno BL, Nabeth P, Kersteins B, et al. The reemergence of Ebola hemorrhagic fever, Democratic Republic of the Congo, 1995. Commission de Lutte contre les Epidémies à Kikwit. J Infect Dis 1999;179 Suppl 1:S76-86.
7. Tartari E, Allegranzi B, Ang B, Calleja N, Collignon P, Hopman J, et al. Preparedness of institutions around the world for managing patients with Ebola virus disease: an infection control readiness checklist. Antimicrob Resist Infect Control 2015;22:1-11.

Appendix 1
Assessment Checklist

Box 1: Response

1. Clinical Management

a. Clear command and control line for the clinical management of the suspect case
b. System to carry out temperature screening of patients.
c. System to identify febrile patients and suspect case. (TRIAGE)
d. System to achieve immediate and effective local isolation by physically isolating the suspect case from other patients by at least 1 metre.
e. System to activate the Infection Control Response Team (team competent and trained to handle the patient).
f. System to transfer and hand over clinical management to ICRT (if applicable)
g. System to reduce exposure to staff (minimum number required to attend to patient)

2. Infection Control Response Team (ICRT)

a. System to pre-determine composition of the ICRT. (EMD is adequately staffed with personnel trained in PPE per shift)
b. Name list with contact particulars of identified ICRT personnel. (System to handover to isolation ward/ ID team after office hours)
c. ICRT staff are adequately protected.
d. System to reduce exposure to ICRT staff (eg minimum number required to attend to patient)
e. System for ICRT to assess infection control risk and initiate appropriate infection controls for the ward and hospital.
f. System to manage and minimise movement of patients in and out of the ward.
g. System to restrict entry of visitors to ward.
h. Demarcation of area to restrict patients/visitors movement (e.g. signages present, perimeter drawn)
i. Appropriate PPE donned to handle suspect patient
j. Alcohol hand-rubs and sanitisers present to staff
k. System to obtain clinical sample from suspect case.
l. System to ensure clinical sample is handled according to appropriate risk group of pathogen.
m. System to transport clinical sample to internal or external laboratory for confirmatory analysis.
n. System to receive result of confirmatory analysis
o. System to communicate to the Hospital Ops Centre and management, information on the detection of the suspect case.
p. System to manage the normal operations together with the detection of the suspect case.
q. System to do contact tracing.
r. System to manage patients and staff (eg, fever monitoring and further management).
s. System to gather exposure history, relevant contact details and check health status of Next-of-Kin
t. System to communicate with Next-of-Kin to inform them of the patient's/case's condition
u. System to ensure cases requiring radiology studies and other procedures are transferred with proper infection control precautions.

3. Intra-hospital transfers

a. Flow of cases out of ward via controlled disposition point.
b. System to notify Isolation Ward or Intensive Care Unit of the transfer prior to actual disposition from the ward.
c. System to assign trolley and management team prior to actual disposition from the ward.
d. Transfer routes are pre-planned.
e. System to minimise contamination of environment and other persons during transfer.
f. Supply of PPE for paramedical staff
g. System to track movement of case e.g. radiology department or operating theatre

4. Inter-hospital Transfers

a. System to notify receiving hospital of transfer prior to actual disposition from the hospital.
b. System to transfer suspect/confirmed case to receiving hospital.
c. Case is accompanied by the required medical staff during the transfer
d. Staff carrying out the transfer are adequately protected.

Box 1: Response (Con't)

e. Transfer routes are pre-planned.
f. System to ensure the transfer and hand-over of clinical management documentation together with the case.
g. System to document transfer.
h. System to minimise contamination of environment and other persons during transfer.
i. System to disinfect equipment (including vehicle), and persons involved in the transfer.

5. Disposal and Decontamination

a. System to carry out decontamination of the environment.
b. System to dispose biohazardous wastes.
c. System to protect cleaning staff.
d. System to store reusable equipment prior to being sent for cleaning.
e. System to transport, clean, and disinfect reusable equipment.
f. System to manage dead bodies
g. System to ensure bodily wastes are treated appropriately

Box 2: Personal Infection Control Practice

1. PPE

a. System to ensure proper donning and doffing of PPE.
b. Adequate supply of PPE.
c. Mechanism to request for appropriate additional PPE (for example gloves, gowns) to provide adequate protection.
d. Proper disposal of PPE after use.
e. System to manage spills on PPE/breach of PPE

2. Hand Hygiene

a. Standard for hand hygiene clearly defined.
b. Hand hygiene meets standard for infection control.
c. Hand washing and drying facilities for staff are within easy access.

Box 3: Communications

a. Pre-planned communication lines between the Ward, Isolation Ward, Intensive Care Units, Hospital Operations Centre, and with other departments within the hospital.
b. Telephone lists of ICRT, Isolation Ward, Hospital Operations Centre, and other departments.
c. Adequate communication means (for example cordless phones, fax machines, walkie-talkies/mobitalk sets, email) to ensure command, control and communication.
d. System to manage public reaction to knowledge of a suspect case
e. System to manage Visitor policy if there are changes
f. System to communicate to the patients/family members on the situation in the ward.
g. System to gather exposure history, relevant contact details and check health status of Next-of-Kin
h. System to communicate with Next-of-Kin to inform them of the patient's/case's condition
i. System to escalate for decision-making
j. System to ensure adequate covering of key appointment holders during their absence
k. System to manage the media / press
l. System to disseminate information for awareness

Box 4: Surveillance and Epidemiology

a. System to report to Ministry of Health unusual health events especially in cases with travel history to EVD affected countries.
b. System to ensure timely notification and update on progress of cases.
c. System to pre-determine composition of epidemiology team.
d. Name list with contact number of epidemiology team staff which the hospital has pre-identified for deployment.
e. System to rotate the staff in the event of a prolonged incident.

Box 5: Contact Tracing

1. Team Setup

a. System to pre-determine composition of Hospital Contact Tracing (HCT) Team.
b. Point of Contact (POC) has been identified.
c. Name list with contact number of HCT Team personnel which the hospital has pre-identified for deployment.
d. Well-defined tasks and responsibilities for HCT Team staff.
e. System to rotate the POC and HCT Team staff in the event of a prolonged incident.

2. Activity Mapping

a. System to trigger activity mapping.
b. System to ensure correct template is used and filled in appropriately.
c. System to ensure that activity map is submitted to Ministry of Health on time and is complete.

3. Hospital Contact Tracing Template

a. System to trigger hospital contact tracing.
b. System to ensure correct template is used and filled in appropriately.
c. System to capture HCW contacts.
d. System to capture patient contacts.
e. System to capture visitor contacts.
f. System to ensure contact tracing information is submitted to MOH on time and is complete.
g. System to monitor health status of HCW contacts
h. System to minimise risk of cross contamination by HCW contacts

Original Article

Psychosocial Factors, Knowledge and Attitudes Influencing Skin and Heart Valve Donation among Healthcare Professionals in Singapore

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Abstract

Introduction: In Singapore, tissue donation is covered under the Medical (Therapy, Education and Research) Act. The objective of this study is to review the demographic and psychosocial factors, which may cause hesitation/unwillingness amongst healthcare professionals towards tissue donation. Materials and Methods: A survey comprising 18-items was conducted at the Singapore General Hospital and National Heart Centre Singapore. A total of 521 individuals participated in the survey. Descriptive statistics were performed for the demographic profiles of participants, the factors leading to the support of tissue donation, reasons for hesitation/reluctance to donate tissue and motivating factors to discuss tissue donation with next-of-kin. Pearson's chi-square and Fisher's exact tests were employed to assess possible association between various factors and support towards tissue donation. Analyses were performed using Statistical Package for Social Sciences V.21.0 software. Results: A total of 64.9% of participants had heard about skin donation; 48.9% had heard about heart valve donation; 4.5% were tissue pledgers. The primary reason for pro-donation was the altruism of "improving someone's quality of life". However, a majority stated they "can decide this in the later part of life" as their main reason for hesitation; 82.3% were willing to discuss their tissue donation wish with next-of-kin, while 53.1% were likely to make the decision of donation on behalf of their deceased next-of-kin. Conclusion: Results highlighted important psychosocial and professional factors that influence the hesitation/reluctance towards donation. Hence, there is a need to re-strategise educational efforts in accordance with the target audiences and address specific misconceptions and concerns.

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Key words: Heart valve banking, Tissue donation, Skin allografts, Skin banking

Introduction

In Singapore, the donation of heart valves and skin is covered under a consent-based opt-in legislation called the Medical (Therapy, Education and Research) Act (MTERA). This Act allows individuals who wish to pledge their organs and tissues upon death for transplant, research or education purposes to opt-in by completing a pledge form. MTERA also gives family members of the deceased the right to donate his/her organs and tissues upon death if they wish to do so.[1] It relies solely on the goodwill of individuals to volunteer and donate their own or their next-of-kin's organs/tissues as an altruistic act.

Though the Act has been in existence for the past 42 years, the organ and tissue donation rate has remained dismal. In 2012, there were only 67,274 organ pledgers in the Organ Donor Registry out of the 5.3 million residents (1.3%) of Singapore.[2]

Studies have identified several external factors that influence the personal attitudes of individuals towards organ donation and transplantation. These external factors include experiential, educational, social, cultural and religious factors.[3,4] The attitudes of healthcare professionals have been linked to low level of knowledge pertaining to organ/tissue donation, resulting in limited donor pool.[5]

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It is vital to address the knowledge deficits of healthcare professionals and understand their attitude towards organ/tissue donation. This is crucial as most of them assist in identifying potential donors and educating the public and fellow colleagues about donation. Should they undertake their roles effectively, this will have a direct impact on increasing the number of donors.[3,6] However, to date, limited research has been conducted to explore the knowledge and attitude of healthcare professionals in Singapore towards tissue donation. Therefore, this survey was conducted with the aim of reviewing the demographic and psychosocial factors that may influence support or hesitation/reluctance towards tissue donation, the level of knowledge about tissue donation and possibly identify the areas for improvement. Results collated will be used to formulate publicity strategies for tissue banks, so as to provide adequate education addressing knowledge gaps to the healthcare professionals.

Materials and Methods

Study Population

In 2012, a survey comprising 18-items was conducted among healthcare professionals—doctors, nurses, allied health and support service staff, who play administrative, ancillary and non-clinical positions—working at the Singapore General Hospital and National Heart Centre Singapore (Appendix 1). The sample size of 521 participants was calculated in accordance with the occupation ratio of these 2 institutions.[7]

Questionnaire-based Data Collection

Data was collated through an anonymous survey questionnaire that was distributed to the department through the individual departments' supervisors. The survey questionnaire was developed based on questions from other similar studies. Furthermore, certain modifications were made in the questionnaire so as to reflect relevant content as per our local context. A pilot study, results of which were not taken into account, was subsequently conducted among a group of healthcare colleagues to assess the clarity, ease of interpretation and functionality of the questionnaire. After further refinement of the questionnaire, it was circulated among the healthcare professionals. Informed consent was assumed when survey participants completed and returned the questionnaire. Ethical consideration was achieved by anonymity as participants were only required to identify their current roles in their institutions and no other personal identifier was solicited or recorded.

Data Analysis

Descriptive statistics were performed for the demographic profiles of the participants, factors leading to support and consent towards tissue/organ donation, reasons for hesitation or reluctance for tissue donation, and factors motivating participants to discuss tissue donation with family members and get their consent. Pearson's chi-square test and Fisher's exact test were employed to assess the possible association between various factors and support towards skin and heart valve donation, and the desire to willingly pledge to donate skin and/or heart valves. To identify predictors of willingness to donate and being a pledger, binary logistic regression modelling was performed. Input variables that showed potential association with outcome in Pearson's chi-square or Fisher's exact test with P value <0.1 were included in multivariate analysis. All tests with P value <0.05 were deemed significant. Analyses were performed using IBM Statistical Package for Social Sciences (SPSS) V.21.0 software (IBM, Armonk, NY).

Results

A total of 521 participants were randomly surveyed, of which, 450 (86.4%) completed and returned the survey (Table 1).

Knowledge of Skin and Heart Valve Donation

In the first part of this study, results revealed that there were more participants who had heard about skin donation (64.9%) than heart valve donation (48.9%). However, although a majority of participants claimed to support tissue

Table 1. Demographic Characteristics and Education Profile of Study Subjects

Demographics Information	% of Respondents
Gender	
Male	14.9
Female	82.7
Unknown	2.4
Age group	
18 – 24	28.4
25 – 34	42.2
35 – 44	15.8
45 – 54	10.3
≥55	3.1
Race	
Chinese	58.7
Malay	16.2
Indian	9.3
Other	12.7
Unknown	3.1

ITE: Institute of Technical Education; NITEC: National Institute of Technical Education Certificate

Table 1. Demographic Characteristics and Education Profile of Study Subjects (Con't)

Demographics Information	% of Respondents
Nationality	
Singaporean	72.2
Permanent resident	12.2
Non-resident	15.3
Unknown	0.2
Religious affiliation	
Catholicism/Christianity	30.4
Buddhism	25.3
Hinduism	5.1
Islam	20.9
Others	17.8
Unknown	0.4
Highest level of education	
No formal education to lower secondary	0.2
Secondary or equivalent	9.3
A-levels or equivalent	1.1
National ITE certificate (NITEC) or higher NITEC	6.7
Polytechnic diploma or equivalent	22.9
Higher/advanced diploma	6.4
Bachelor degree	42.4
Postgraduate diploma or postgraduate degree	10.4
Unknown	0.4
Current role	
Nurse	51.3
Allied health	16.9
Doctor	8.4
Administration/ancillary/support	23.3
Involvement in transplant work	
No	66.4
Patient care	31.6
Communications/publications	0.4
Research	0.7
Others	0.4
Unknown	0.4

ITE: Institute of Technical Education; NITEC: National Institute of Technical Education Certificate

Table 2. Source of Information and Support and Willingness towards Tissue Donation

Survey Questions	% of Respondents
Heard, seen or read about skin donation	
Yes	64.9
No	34.4
Unknown	0.7
Heard, seen or read about heart valve donation	
Yes	48.9
No	50.4
Unknown	0.7
Support the donation of human skin for transplantation	Mean = 1.56, SE = 0.035, SD = 0.74
Support	55.9
Somewhat support	35.2
Somewhat oppose	6.0
Oppose	2.9
Support the donation of human heart valves for transplantation	Mean = 1.55, SE = 0.033, SD = 0.70
Support	54.9
Somewhat support	37.5
Somewhat oppose	5.4
Oppose	2.2
Signed up as a tissue pledger	
Yes	4.5
No	95.5
Willingness to donate skin upon death	
Very willing	38.1
Somewhat willing	35.9
Somewhat unwilling	12.7
Very unwilling	13.4
Willingness to donate heart valves upon death	
Very willing	41.1
Somewhat willing	35.6
Somewhat unwilling	11.6
Very unwilling	11.8
If skin and heart valves were legislated under presumed consent, will you:	
Opt out on both tissues	0
Opt out on skin donation	18.2
Opt out on heart valve donation	9.3
Do nothing, as I support tissue donation	5.8
Do nothing, other reasons*	65.8

*Majority of the reasons given are ambiguous intention or wish to know more information about donation.

donation, only 4.5% of them actively registered as a tissue pledger; 76.7% indicated that they are very or somewhat willing to donate heart valves as compared to donate skin tissue (74%). It was also found that if skin and heart valves were legislated under presumed consent, most of the participants (65.8%) would do nothing to change their status, and more participants would opt out of skin donation (18.2%) as compared to heart valve donation (9.3%) (Table 2).

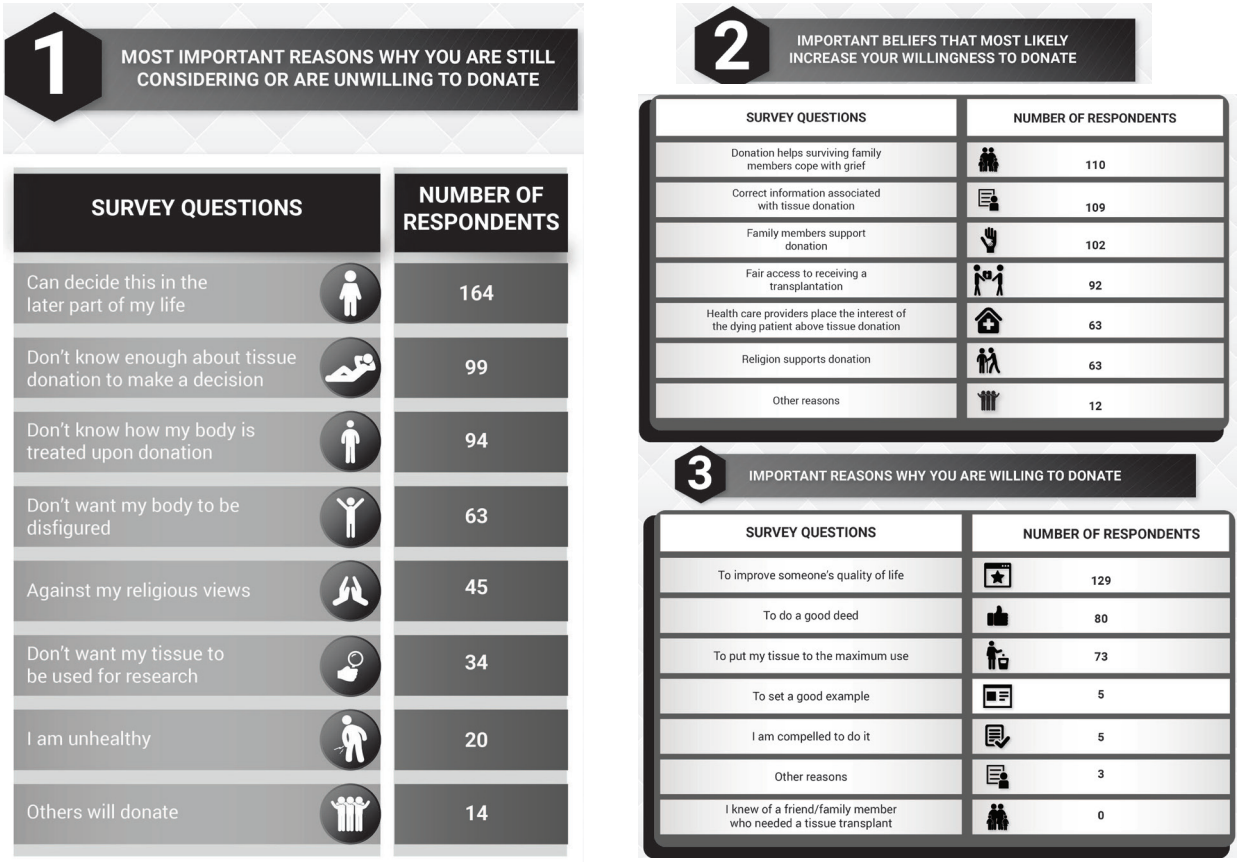

Fig. 1. Reasons for willingness and hesitation/unwillingness for tissue donation.

Attitudes towards Tissue Donation

The 3 main reasons why the participants were willing to donate their tissues were the altruistic intention of "improving someone's quality of life", "doing a good deed" and "putting my tissue to the maximum use". However, of those who were unwilling or still considering tissue donation, the majority stated 3 causes for their hesitation, namely, "I can decide this in the later part of my life", "don't know enough about tissue donation to make a decision" and "don't know how my body is treated upon donation." They indicated that the 3 important beliefs that will most likely increase their willingness to donate tissue were "donation helps their surviving family members to cope with grief", if they were given "correct information associated with tissue donation" and if their "family members support donation" (Fig. 1).

Willingness to Discuss with Family Members about Tissue Donation

A total of 82.3% of the participants were very or somewhat willing to discuss their wish to donate tissue with their family members; 53.1% were very or somewhat likely to make the decision of tissue donation on behalf of their deceased family members, in the event that they did not know the latter's wish about tissue donation. However, if their deceased family member had expressed interest in tissue donation upon death, 87.8% would honour the deceased's wish and would be very or somewhat likely to donate their tissues. For those who were unwilling to donate their deceased family members' tissues, none of the proposals of assistance with regard to hospitalisation or funeral expenses or priority in receiving tissue transplantation among others would increase their willingness to donate (Fig. 2).

Support for Skin Donation

In univariate analysis, support for skin donation was found to be statistically significantly associated with race, higher level of education, religious affiliation, current role, involvement in transplant work, having seen/read/heard about skin donation, willingness to discuss about donation, likeliness to donate family member's skin and wish to opt out if there was a change in legislation governing tissue donation. Participants with a degree or higher were reported to be 1.07 times more likely to support skin donation

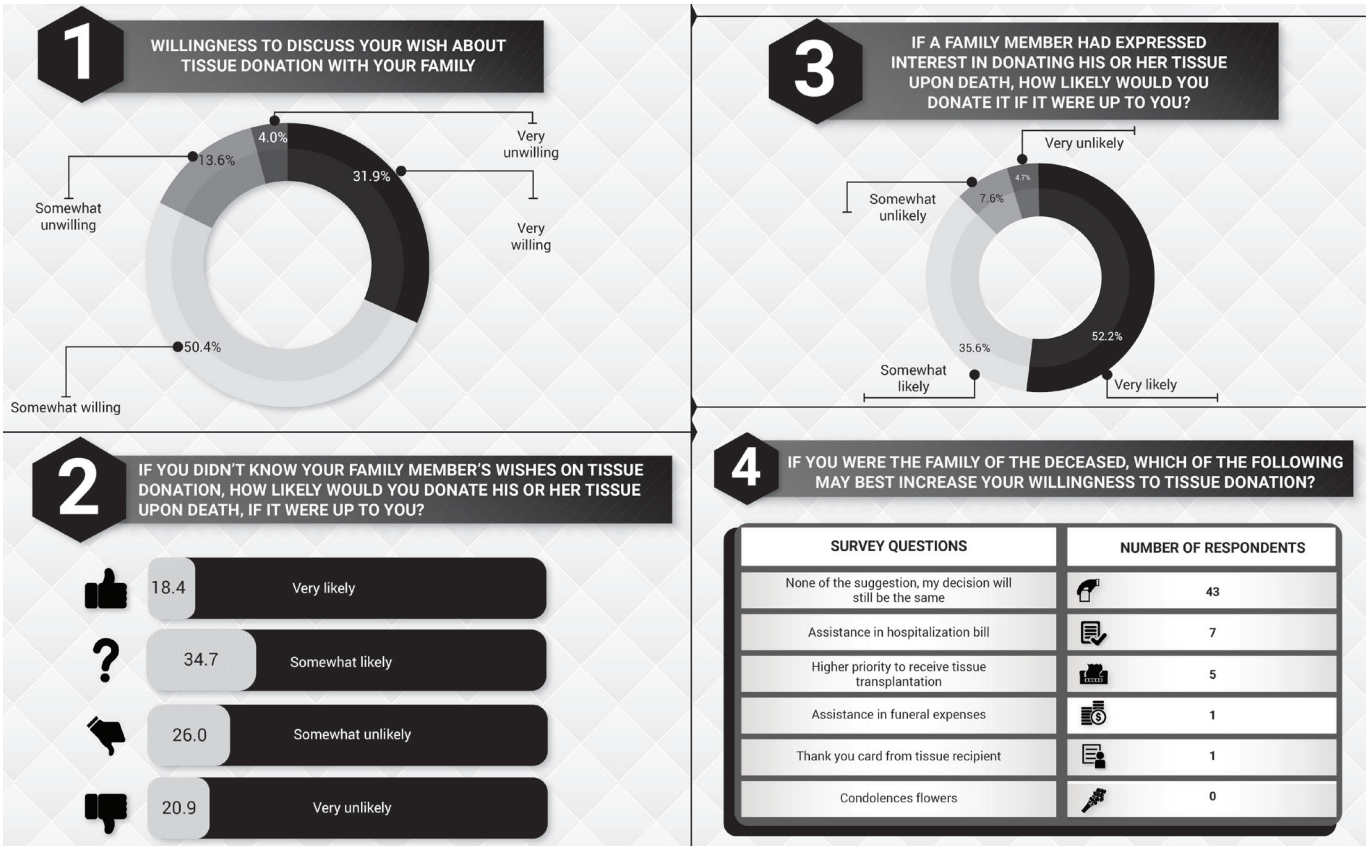

Fig. 2. Discussion of tissue donation with family members.

compared to those with other types of education levels (95% CI, 1.01 to 1.14; $P = 0.02$).

However, in multivariate analysis, after adjustment of all demographic factors and willingness to discuss about tissue donation, as well as, likeliness to donate family member's tissue, support for skin donation was found to be statistically significantly associated with current role (nurse versus others), willingness to discuss about skin donation with family members, likeliness to donate family member's tissue after knowing his/her wish to donate and change in legislation. After adjustment, non-nursing participants were 3.17 times more likely to report their support for skin donation compared to nursing respondents (95% CI, 1.27 to 7.93; $P = 0.01$) (Table 3).

Support for Heart Valve Donation

In univariate analysis, support for heart valve donation was found to be statistically significantly associated with race, higher level of education, religious affiliation, current role, involvement in transplant work, having seen/read/heard about heart valve donation, willingness to discuss about donation, likeliness to donate family member's skin and wish to opt out if there was a change in legislation governing tissue donation. Respondents with a degree or higher were reported to be 1.06 times more likely to support heart valve donation compared to those with other types of education levels (95% CI, 1.0 to 1.12; $P = 0.048$).

However, in multivariate analysis, after adjustment of all demographic factors and willingness to discuss about tissue donation, as well as, likeliness to donate family member's tissue, support for heart valve donation was found to be statistically significantly associated with current role (nurse versus others), having seen/read/heard about heart valve donation, likeliness to donate family member's tissue knowing his/her wish to donate and change in legislation and wish to opt out if there was a change in legislation governing tissue donation. After adjustment, non-nursing participants were 3.17 times more likely to report their support for heart valve donation compared to nursing respondents (95% CI, 1.18 to 8.50; $P = 0.02$) (Table 4).

Tissue Pledger, Demographic Factors and Willingness to Donate Tissue

In univariate analysis, being a tissue pledger was found to

Table 3. Association between Support for Skin Donation for Transplantation and Demographic, Educational, Professional and Psychosocial Factors and Willingness in Donation

Factor	Unadjusted		Adjusted	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Nationality				
Singaporean (n = 324)	1.24 (0.52 – 2.98)			
Permanent resident (n = 55)	0.92 (0.29 – 2.92)			
Foreigner (n = 69)	0	0.77	-	
Gender				
Male (n = 66)	0.99 (0.02 – 1.08)			
Female (n = 372)	1*	0.82	-	
Age by group				
18 – 24 (n = 128)	0.74 (0.09 – 6.19)			
25 – 34 (n = 190)	0.84 (0.10 – 6.81)			
35 – 44 (n = 70)	0.82 (0.09 – 7.40)			
45 – 54 (n = 46)	0.63 (0.07 – 5.90)			
≥55 (n = 14)	1	0.98	-	
Race (2 groups, n = 435)				
Chinese (n = 263)	1.08 (1.01 – 1.16)		0.87 (0.24 – 3.06)	
Others (n = 172)	1	0.01	1	0.82
Highest level of education				
Others (n = 210)	1		1	
Degree and higher (n = 237)	1.07 (1.01 – 1.14)	0.02	0.68 (0.27 – 1.69)	0.41
Religious affiliation (2 groups)				
Islam (n = 94)	1		1	
Others (n = 353)	1.16 (1.05 – 1.28)	<0.001	1.80 (0.49 – 6.57)	0.37
Current role (n = 449)				
Nurse (n = 231)	1		1	
Other (n = 218)	1.09 (1.02 – 1.15)	0.007	3.17 (1.27 – 7.93)	0.014
Involvement in transplant work				
No (n = 283)	1		1	
Yes (n = 150)	1.08 (1.02 – 1.14)	0.008	3.01 (0.96 – 9.43)	0.06
Years working in Outram campus				
0 – 5 years (n = 305)	1			
>5 years (n = 138)	1.05 (0.99 – 1.11)	0.15	-	
Have you seen, read or heard of skin donation?				
No (n = 155)	1		1	
Yes (n = 292)	1.09 (1.02 – 1.17)	0.008	2.16 (0.97 – 4.82)	0.06
Are you willing to discuss about tissue donation with your family?				
No (n = 79)	1		1	
Yes (n = 368)	1.34 (1.16 – 1.55)	<0.001	3.12 (1.19 – 8.22)	0.02
If you didn't know your family member's wishes on tissue donation, how likely would you donate his or her tissues upon death, if it were up to you?				
Unlikely (n = 211)	1		1	
Likely (n = 238)	1.15 (1.08 – 1.22)	<0.001	2.05 (0.69 – 6.09)	0.19
If a family member had expressed interest in donating his or her tissues upon death, how likely would you donate if it were up to you?				
Unlikely (n = 55)	1		1	
Likely (n = 394)	1.49 (1.22 – 1.82)	<0.001	3.23 (1.20 – 8.64)	0.02
If skin and heart valves were legislated under presumed consent, will you:				
Opt out (n = 124)	1		1	
Do nothing (n = 321)	1.17 (1.07 – 1.27)	<0.001	2.66 (1.19 – 5.92)	0.02

*Reference group.

Table 4. Association between Support for Heart Valve Donation for Transplantation and Demographic, Educational, Professional and Psychosocial Factors and Willingness in Donation

Factor	Unadjusted		Adjusted	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Nationality				
Singaporean (n = 323)	0.93 (0.34 – 2.53)			
Permanent resident (n = 55)	0.99 (2.54 – 3.90)			
Foreigner (n = 69)	1	0.98	-	
Gender				
Male (n = 66)	0.98 (0.90 – 1.06)			
Female (n = 371)	1*	0.61	-	
Age by group				
18 – 24 (n = 128)	2.36 (0.64 – 10.78)			
25 – 34 (n = 190)	4.91 (1.18 – 20.44)			
35 – 44 (n = 70)	2.86 (0.62 – 13.18)			
45 – 54 (n = 46)	3.91 (0.69 – 22.09)			
≥55 (n = 14)	1	0.24	-	
Race				
Chinese (n = 262)	1.06 (1.01 – 1.13)		0.43 (0.09 – 1.99)	
Others (n = 172)	1	0.04	1	0.28
Highest level of education				
Others (n = 210)	1		1	
Degree and higher (n = 236)	1.06 (1.00 – 1.12)	0.048	0.83 (0.32 – 2.18)	0.71
Religious affiliation (2 groups)				
Islam (n = 94)	1		1	
Others (n = 352)	1.13 (1.03 – 1.23)	0.002	2.26 (0.48 – 10.62)	0.30
Current role (n = 449)				
Nurse (n = 231)	1		1	
Other (n = 217)	1.06 (1.01 – 1.12)	0.031	3.17 (1.18 – 8.50)	0.02
Involvement in transplant work				
No (n = 297)	1		1	
Yes (n = 150)	1.08 (1.03 – 1.13)	0.004	2.77 (0.79 – 9.59)	0.11
Years working in Outram campus				
0 – 5 years (n = 305)	1			
>5 years (n = 137)	1.04 (0.98 – 1.09)	0.24	-	
Have you seen, read or heard of heart valves donation?				
No (n = 226)	1		1	
Yes (n = 220)	1.08 (1.02 – 1.13)	0.005	2.77 (1.32 – 9.09)	0.01
Are you willing to discuss about tissue donation with your family?				
No (n = 79)	1		1	
Yes (n = 367)	1.21 (1.08 – 1.37)	<0.001	2.08 (0.76 – 5.74)	0.15
If you didn't know your family member's wishes on tissue donation, how likely would you donate his or her tissues upon death, if it were up to you?				
Unlikely (n = 210)	1		1	
Likely (n = 238)	1.12 (1.06 – 1.19)	<0.001	2.79 (0.81 – 9.60)	0.10
If a family member had expressed interest in donating his or her tissues upon death, how likely would you donate if it were up to you?				
Unlikely (n = 55)	1		1	
Likely (n = 393)	1.38 (1.16 – 1.65)	<0.001	4.38 (1.54 – 12.48)	0.006
If skin and heart valves were legislated under presumed consent, will you:				
Opt out (n = 124)	1		1	
Do nothing (n = 320)	1.13 (1.04 – 1.22)	<0.001	1.87 (0.79 – 4.44)	0.15

*Reference group.

be statistically significantly associated with gender, current role and involvement in transplant work. Participants who were involved in transplant work were reported to be 2.43 times more likely to support tissue donation compared to those who were not involved (95% CI, 1.03 to 5.73, P = 0.05). However, in multivariate analysis, after adjusting all demographic factors, support for tissue donation was found to be non-statistically significant due to small sample size (Table 5).

The findings of the second part of the study were reported in the 'Evaluation of the effectiveness of the different modes of publicity used for tissue donation among healthcare professionals in Singapore'.[8]

Discussion

The results of the current survey identified specific areas of concerns. Firstly, the number of healthcare professionals who had heard about skin donation was more than those who had heard about heart valve donation. This may be because the skin bank was established 11 years prior to the cardiovascular homograft bank.

Secondly, most healthcare professionals would opt out of skin donation as compared to heart valve donation if both tissues were legislated under presumed consent. This can probably be attributed to misconceptions existing among people regarding skin donation; some of these misconceptions, which we gathered informally through awareness talks with different groups of audiences include: recovery of skin from the entire body, fear of disfigurement and bloodiness, and the body will not be presentable during an open casket funeral. Unlike the American and European societies, who are generally more open to donation, our society comprising predominantly of Chinese and Malay societies have traditional cultural values, which result in greater antipathy towards organ/tissue donation.[9] This was evident in various studies, for instance, 27% of 2930 Chinese participants would not consent to donate their own organs after their passing due to the traditional Chinese belief of the necessity to have an intact body after death for a good afterlife.[10,11] Another evidence of traditional cultural values influencing people's decision to donate tissue/organs is the statistics obtained from 2000 to 2010 by National Transplant Resource Centre, Kuala Lumpur, which reported that donation among the Malay community (the dominant ethnic group in Malaysia) contributed to only 6.36% of the total organ donation as compared to 61.86% by Chinese and 31.78% by Indians; the study cited the Malay community's perception that their religion, Islam, did not permit them to donate tissue/organs as the primary reason for their low donation rates.[12]

Thirdly, although most healthcare professionals support tissue donation, not many of them have registered to pledge for tissue donation. This attitude of healthcare professionals may be attributed to several reasons: 1) lack of awareness that tissue donation is by opt-in system (MTERA), and not an opt-out system (HOTA) for organs; 2) lack of information about what is required of them to join the registry; and 3) signing up as a pledger is not a priority.[13] With regard to the last reason, it might have been the same reason that caused hesitation or reluctance to donate organs/tissues—the procrastinating mindset of "can decide later in my life". This may suggest fear, hesitation and reluctance to think about death. Therefore, this mindset leads participants to refrain from registering as tissue donors, as it requires them to face their own mortality.[3]

Another factor that may have attributed to the high rate of support towards donation, while, disproportionately low pledger rate is a behavioural phenomenon called deterioration of support as one moves from abstract support to the concept of donation to a more personal and concrete commitment. The most commonly cited reasons for willingness to donate are altruistic concerns of "improving someone's quality of life" and "doing a good deed". However, we are uncertain if such self-reports may reflect a tendency to provide socially desirable responses although their anonymity is upheld.[14]

Fourthly, as reported by McGlade et al, the choice of a caring profession such as nursing does not equate to a larger degree of altruism and more support to tissue donation or pro-donation behaviour.[3] This observation was consistent in the Singapore context as well, as participants who are nurses were 3 times less likely to donate both skin and heart valves. Ideally, critical care nurses (being the main care provider for patients, emotional support for family members, and the key to identifying potential donors) should have detailed knowledge of tissue donation. In this way, they will understand its benefits and the clinical, technical, ethical and legal aspects of donation. If nurses are not supportive due to various reasons or are not fully educated about tissue donation and transplantation, the situation of organ and tissue shortages will be difficult to address. Hence, such education should be incorporated into mandatory training in nursing school's curriculum or new staff orientation programme.[15]

Fifthly, the paramount role family members play in influencing the attitude and decision-making process of individuals with regard to tissue donation was highlighted. This may be reflective of the stronger societal family values in Singapore.[16] Strong family influence in tissue donation is a significant factor in two aspects: firstly, the willingness to donate tissue/organs increases if family members are pro-donation; secondly, since most healthcare professionals are "silent" or "passive" supporters of tissue donation, it is

Table 5. Association between Being a Tissue Pledger and Demographic Factors and Willingness to Donate

Factor	Unadjusted		Adjusted	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Nationality				
Singaporean/permanent resident (n = 379)	1			
Foreigner (n = 69)	0.30 (0.04 – 2.25)	0.33	-	-
Gender				
Male (n = 66)	2.60 (1.02 – 6.60)		0.45 (0.12 – 1.62)	
Female (n = 372)	1*	0.05	1	0.22
Age by group				
18 – 44 (n = 388)	0.88 (0.26 – 2.90)			
>45 (n = 60)	1	0.74		
Race				
Malay (n = 73)	1			
Others (n = 362)	3.63 (0.49 – 26.76)	0.22	-	-
Highest level of education				
ITE and below (n = 73)	3.17 (0.39 – 25.20)			
Diploma, advanced diploma, A-level (n = 137)	0.63 (0.25 – 1.58)	0.25	-	-
Degree and higher (n = 237)	1			
Religious affiliation (2 groups)				
Islam (n = 94)	1		1	
Others (n = 353)	5.06 (0.69 – 37.31)	0.09	0.31 (0.04 – 2.53)	0.28
Current role (n = 449)				
Doctor/surgeon (n = 37)	0.16 (0.03 – 0.91)		0.24 (0.02 – 2.72)	
Nurse (n = 231)	0.54 (0.11 – 2.59)		0.29 (0.03 – 2.53)	
Allied health (n = 76)	0.23 (0.04 – 1.15)		0.19 (0.02 – 1.69)	
Administration/ancillary/support (n = 105)	1	0.07	1	0.51
Involvement in transplant work				
No (n = 298)	1		1	
Yes (n = 150)	2.43 (1.03 – 5.73)	0.05	0.70 (0.25 – 19.6)	0.50
Have you seen, read or heard of skin donation?				
No (n = 155)	1			
Yes (n = 292)	1.15 (0.45 – 2.97)	1.00	-	-
Have you seen, read or heard of heart valves donation?				
No (n = 227)	1		1	
Yes (n = 220)	2.41 (0.94 – 6.15)	0.07	0.47 (0.16 – 1.38)	0.17
Are you willing to discuss about tissue donation with your family?				
No (n = 79)	1			
Yes (n = 368)	4.08 (0.55 – 30.3)	0.23	-	
If you didn't know your family member's wishes on tissue donation, how likely would you donate his or her tissues upon death, if it were up to you?				
Unlikely (n = 211)	1		1	
Likely (n = 238)	2.66 (0.90 – 7.19)	0.06	0.49 (0.17 – 1.44)	0.19
If a family member had expressed interest in donating his or her tissues upon death, how likely would you donate if it were up to you?				
Unlikely (n = 55)	1			
Likely (n = 394)	Not available†	0.15	-	-

ITE: Institute of Technical Education

*Reference group.

†No odds ratio (OR) as 1 category had 0 pledger.

all the more crucial that this intention be communicated to family members, as they will be the ones who will execute the wishes of their deceased loved ones. However, it is not in the Asian culture to discuss about death-related issues with family members, as it is regarded inauspicious. As a result, it is not uncommon for relatives to be unaware of the wishes of their family members prior to their death.[17] More than half of healthcare professionals surveyed stated that if they were uncertain about their deceased family member's wishes, they would be less likely to make the decision of donation if it was up to them. Previously, similar trends were also reported internationally.[3] In instances when family members decide not to donate, none of the incentives such as financial assistance in hospitalisation and funeral expenses or higher priority in receiving transplantation would change their decision. Conversely, if they know the deceased family members' intentions, a majority of family members would honour their wishes and consent to donation. Most healthcare professionals were willing to discuss the topic of tissue donation with their family members. During actual ground work, a potential donor's family member suggested to our transplant coordinator that our approach was incorrect; she mentioned that the coordinator should approach the potential donor when he was still alive to ascertain his wish with regard to tissue donation in the presence of other family members. Although this approach of broaching the subject of tissue donation to a potential donor during his/her final moments of life is impractical and even unethical, this suggestion reinforced the importance of communication about tissue donation during family discussions when one is healthy. Another approach is to facilitate familial decision and increase familial support towards tissue donation in the event of the patients' demise by integrating tissue donation into the end-of-life care of the patients.[11]

The limitations of this study are non-participation bias and convenience element, which leads to the selection of only 2 hospitals for participation. Ideally, the study subjects should consist of a randomised sample from all hospitals in Singapore. It is noteworthy that despite high education levels and being in the healthcare industry, most healthcare professionals still had inadequate knowledge about tissue donation. This lack of knowledge about tissue donation can be judged from the significant reasons for their hesitation or reluctance to donate, which they cited as: "don't know enough about tissue donation to make a decision" and "don't know how my body is treated upon donation". Therefore, through this study, a more comprehensive understanding of the psychosocial factors and attitudes of healthcare professionals, which influence tissue donation, can be gained. Thus, it will be more effective if tissue banks re-strategise educational efforts in accordance with the target audiences, addressing areas of personal motivation of these potential donors to increase willingness to donate tissue/organs,[18] and clarifying specific misconceptions and concerns that they may have. This is consistent with the belief that "correct information associated with tissue donation" will increase the willingness to donate tissue/organs.

REFERENCES

1. Ministry of Health, Singapore. The Medical (Therapy, Education, Research) Act (MTERA). 2010. Available at: https://www.moh.gov.sg/content/moh_web/home/legislation/legislation_and_guidelines/the_medical_therapyeducationandresearchactmtera.html. Accessed on 27 January 2015.
2. National Organ Transplant Unit. Annual Report 2012. Singapore: Ministry of Health, 2012.
3. McGlade D, Pierscionek B. Can education alter attitude, behaviour and knowledge about organ donation? A pretest-post-test study. BMJ Open 2013;3:e003961.
4. Kent B. Psychosocial factors influencing nurses' involvement with organ and tissue donation. Int J Nurs Stud 2002;39:429-40.
5. Akgün S, Tokalak I, Erdal R. Attitudes and behaviour related to organ donation and transplantation: a survey of university students. Transplant Proc 2002;34,2009-11.
6. Collins TJ. Organ and tissue donation: a survey of nurse's knowledge and educational needs in an adult ITU. Intensive Crit Care Nurs 2005;21:226-33.
7. Singhealth annual report 2010. Singapore Health Services. Available at: http://www.singhealth.com.sg/AboutSingHealth/CorporateOverview/AnnualReports/Pages/singhealth-annual-report-fy2010.aspx. Accessed on 27 January 2015.
8. Heng WL, Tham I, Yick JL, Chiang IY, Seck T. Evaluation on the effectiveness of the different modes of publicity for tissue donation among healthcare professionals in Singapore. Transplant Rep 2016;1:103.
9. Goh GBB, Mok ZW, Mok ZR, Chang JPE, Tan CK. Organ donation: what else can be done besides legislature? Clin Transplant 2013;27:E659-64.
10. Wang W, Tian H, Yin H, Liu H, Zhang XD. Attitudes towards organ donation in China. China Med J 2012;125:56-62.
11. Kwek TK, Lew TWK, Tan HL, Kong S. The transplantable organ shortage in Singapore – has implementation of presumed consent to organ donation made a difference? Ann Acad Med Singapore 2009;38:346-53.
12. Noordin N, Zakaria Z, Aminuddin A, Yaacob A, Hilmie MZ, Daud MS, et al. Organ donation among Malaysian: The Malay dilemma toward social development. Asian Social Science 2012;8:8-15.
13. Coad L, Carter N, Ling J. Attitudes of young adults from the UK towards organ donation and transplantation. Transplant Res 2013;2:9.
14. Mclntyre P, Barnett MA, Harris RJ, Shanteau J. Psychological factors influencing decisions to donate organs. Adv in Consumer Res 1987;14:331-4.
15. Jawoniyi OO, Gormley K. How critical care nurses' roles and education affect organ donation. Br J Nur 2015;24:698-700.
16. Yew YW, Saw SM, Pan JCH, Shen HM, Lwin M, Yew MS, et al. Knowledge and beliefs on corneal donation in Singapore adults. Br J Ophthalmol 2005;89:835-40.
17. Heng WL, Seck T, Tay CP, Chua A, Song C, Lim CH, et al. Homograft banking in Singapore: two years of cardiovascular tissue banking in Southeast Asia. Cell Tissue Bank 2013;14:187-94.
18. Chin J, Kwok THX. Ethical challenges in the deceased organ donation programme: Asian perspectives. Indian J Med Ethics 2014;11:139-43.

Appendix 1
Part 1 of the Survey Questionaire on Healthcare Professionals' Beliefs and Willingness on Tissue Donation

Demographics Information:

(a) Nationality: □ Singaporean □ Permanent Resident □ Foreigner

(b) Gender: □ Male □ Female

(c) Age:

□ 18 – 19 □ 20 – 24 □ 25 – 29 □ 30 – 34 □ 35 – 39 □ 40 – 44

□ 45 – 49 □ 50 – 54 □ 55 – 59 □ 60 – 64 □ 65 – 69 □ 70 – 74

□ 75 – 79 □ 80 – 84 □ 85 years and over

(d) Race: □ Chinese □ Malay □ Indian □ Others (Please specify): _____

(e) Religious Affiliation: □ Buddhism □ Catholicism / Christianity □ Hinduism □ Islam

□ Others (Please specify): _____

(f) Highest Level of Education Qualification Obtained:

□ No formal education, lower secondary, or equivalent

□ Secondary i.e.: O' Levels, N' Levels, or equivalent

□ A' Levels, or equivalent

□ National ITE Certificate (NITEC), Higher NITEC, or equivalent

□ Polytechnic Diploma, or equivalent

□ Higher/Advanced Diploma, or equivalent

□ Bachelor Degree

□ Post Graduate Diploma or Degree e.g.: Masters or PhD, or higher

(g) What is your current role : □ Doctor □ Nurse

□ Allied Health: State designation: _____

□ Administration / Ancillary / Support: State designation: _____

(If your answer is Doctor / Nurse / Allied Health proceed to Q(h). Else proceed to Q(i))

(h) How long have you been in this role? _____

(i) How long have you been working at Outram Campus? _____

(j) Are you / have you ever been involved in transplant work? □ Yes □ No

If Yes, what is your major aspect of involvement? :

□ Patient Care □ Communications/Publications □ Research

□ Others (Please specify): _____

Questions:

1. Do you support the donation of human skin for transplantation?

□ Support □ Somewhat Support □ Somewhat Oppose □ Oppose

2. Do you support the donation of human heart valves for transplantation?

□ Support □ Somewhat Support □ Somewhat Oppose □ Oppose

3. Have you signed up as a tissue pledger? □ Yes □ No

4. How willing are you to donate your skin and / or heart valve tissues upon death?

(I) Skin:

□ Willing □ Somewhat willing □ Somewhat unwilling □ Unwilling

(II) Heart Valves:

□ Willing □ Somewhat willing □ Somewhat unwilling □ Unwilling

(If both answers are "Willing", proceed to Question 7. Else, proceed to Question 5.)

5. Select 2 important reasons why you are still considering or are unwilling to donate:

□ I am unhealthy

□ Don't want my tissues to be used for research

□ Can decide this in the later part of my life

□ Others will donate

□ Don't know how my body is treated upon donation

□ Against my religious views

□ Don't know enough about tissue donation to make a decision

□ Don't want my body to be disfigured

□ Others (Please specify): _____

6. Select 2 important beliefs that will most likely increase your willingness to donate:

□ Family members support donation

□ Religion supports donation

□ Donation helps surviving family members cope with grief

□ Fair access to receiving a transplantation (e.g.: regardless of poor / rich)

□ Correct information associated with tissue donation (e.g.: tissue donor families do not pay extra medical bills for the purpose of donation)

□ Health care providers place the interest of the dying patient above tissue donation

□ Others (Please specify): _____ (Proceed to Question 9)

7. Select 2 important reasons why you are willing to donate:

□ To set a good example □ I am compelled to do it

□ To improve someone's quality of life □ To put my tissues to the maximum use

□ To do a good deed □ I knew a friend/ family member who needed tissue transplant

□ Others (Please specify): _____

8. How willing are you to discuss your wish about tissue donation with your family?

□ Very willing □ Somewhat willing □ Somewhat unwilling □ Very unwilling

9. If you didn't know your family member's wishes on tissue donation, how likely would you donate his or her tissues upon death, if it were up to you?

□ Very Likely □ Somewhat Likely □ Somewhat Unlikely □ Very Unlikely

10. If a family member had expressed interest in donating his or her tissues upon death, how likely would you donate if it were up to you?

□ Very Likely □ Somewhat Likely □ Somewhat Unlikely □ Very Unlikely

(If your answer is "Very likely" or "Somewhat likely", proceed to Question 12. Else proceed to Question 11.)

11. If you are the family of the deceased, which of the following may best increase your willingness to tissue donation?

□ Assistance in funeral expenses □ Assistance in hospitalisation bills

□ Thank you card from tissue recipient □ Condolences flowers

□ Higher priority to receive tissue transplantation

□ None of the above, my decision will still be the same

□ Others (Please specify):_____

12. If skin and heart valves were legislated under presumed consent, will you:

□ Opt out on both tissues □ Opt out on skin donation

□ Opt out on heart valve donation □ Do nothing, as I support tissue donation

Original Article

Impact of Direct Cardiovascular Laboratory Activation by Emergency Physicians on False-Positive Activation Rates

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Abstract

Introduction: Door-to-balloon (DTB) time is critical to ST elevation myocardial infarction (STEMI) patients' survival. Although DTB time is reduced with direct cardiovascular laboratory (CVL) activation by emergency physicians, concerns regarding false-positive activation remain. We evaluate false-positive rates before and after direct CVL activation and factors associated with false-positive activations. Materials and Methods: This is a retrospective single centre study of all emergency CVL activation 3 years before and after introduction of direct activation in July 2007. False-positive activation is defined as either: 1) absence of culprit vessel with coronary artery thrombus or ulceration, or 2) presence of chronic total occlusion of culprit vessel, with no cardiac biomarker elevations and no regional wall abnormalities. All false-positive cases were verified by reviewing their coronary angiograms and patient records. Results: A total of 1809 subjects were recruited; 84 (4.64%) identified as false-positives. Incidence of false-positive before and after direct activation was 4.1% and 5.1% respectively, which was not significant ($P = 0.315$). In multivariate logistic regression analysis, factors associated with false-positive were: female (odds ratio (OR): 2.104 [1.247-3.548], $P = 0.005$), absence of chest pain (OR: 5.369 [3.024-9.531], $P < 0.0001$) and presence of only left bundle branch block (LBBB) as indication for activation (OR: 65.691 [19.870-217.179], $P < 0.0001$). Conclusion: Improvement in DTB time with direct CVL activation by emergency physicians is not associated with increased false-positive activations. Factors associated with false-positive, especially lack of chest pain or LBBB, can be taken into account to optimise STEMI management.

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Key words: Cardiac, Catheterisation

Introduction

Door-to-balloon (DTB) time has been shown to be a critical factor in the survival of patients with ST-elevation myocardial infarction (STEMI). A delay in DTB time is associated with higher adjusted risk of in-hospital mortality.[1,2] Consensus guideline recommends a DTB or first medical contact (FMC) to device time goal of 90 minutes or less for STEMI patients to improve their survival.[3] Although direct activation of cardiovascular laboratory (CVL) by emergency physicians without routine cardiology consultation has been shown to reduce DTB time,[4-9] concerns regarding increased rate of false-positive activation with this strategy remain. Factors such as quality metric, potential clinical and financial consequences associated with such false alarms need to be considered too.[10] As such, the main objective of this study is to evaluate the rates of false-positive activation before and after direct CVL activation. We also studied the clinical factors associated with false-positive activations.

Materials and Methods

We conducted a retrospective longitudinal study in a large single tertiary referral centre. Since July 2007, emergency physicians have been autonomously activating the CVL directly for any clinical diagnosis of acute myocardial infarction (AMI) with significant reduction of DTB.[11] The

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eligibility criteria for direct CVL activation by emergency physicians were as follows: ≥2 mm ST elevation in anterior leads for 2 or more contiguous leads or ≥1 mm ST elevation in inferior leads for 2 or more contiguous leads and symptom onset of <12 hours. All patients with a clinical diagnosis of AMI who presented to the emergency department (ED) for a period of 3 years before (1 June 2004 to 1 June 2007) and 3 years after (1 August 2007 to 1 August 2010) were retrospectively included in this study. There was also a 1-month blanking period before and after the start date of direct CVL activation on 1 July 2007.

The exclusion criteria were age ≥80 years old; significant comorbidities or poor premorbid status; contraindications to anticoagulation or antiplatelet therapy; collapsed or in a comatose state; heparin-induced thrombocytopaenia; active gastrointestinal bleed or intravenous contrast allergy.

Data Collection

All patients who had direct CVL activation from the ED were identified via records kept in the CVL. Patient demographics, clinical presentation, 12-lead electrocardiograms (ECGs), treatment and outcomes were then obtained from a combination of patient electronic records, case notes and the National Heart Centre (NHC) Singapore Cardiac Data Bank. All angiographic data were similarly obtained from NHC STEMI database and CVL report. All false-positive activation cases were identified and subsequently verified through the review of their coronary angiograms and patient records by the senior author (HKW). The study protocol was approved by the Centralised Institutional Review Board (IRB) ethics committee.

Definitions

In our study, false-positive activation was defined as either: 1) absence of culprit vessel with coronary artery thrombus or ulceration, or 2) presence of chronic total occlusion of culprit vessel, with no cardiac biomarker elevations to suggest new myocardial infarction (MI) and no regional wall abnormalities in the corresponding cardiac segments.

For each of the verified false-positive cases, the final diagnoses were made based on the following definition.

Early repolarisation variant is defined by J point elevation manifested either as terminal QRS slurring (the transition from the QRS segment to the ST-segment) or notching (a positive deflection inscribed on terminal QRS complex) associated with concave upward ST-segment elevation and prominent T waves in at least two contiguous leads with no elevation of cardiac biomarkers.[12,13] Old MI changes were defined as history of Q wave MI with ST-segment elevation that was either demonstrated on a previous ECG or did not show any ST-segment evolutionary changes with no elevation of cardiac biomarkers.

Perimyocarditis was defined by typical ECG findings of widespread concave ST elevation, elevation of cardiac troponin levels and suggestive clinical history of preceding fever and presence of pericardial rub on examination. Takotsubo stress cardiomyopathy was defined as characteristic apical or mid-ventricular ballooning noted on left ventriculography, reversible left ventricular systolic dysfunction without significant coronary stenosis typically preceded by a stressful event.[14]

Pulmonary embolism (PE) was diagnosed from computed tomographic pulmonary angiography. Left ventricular hypertrophy (LVH) was diagnosed based on ECG voltage criteria. Brugada syndrome is by ECG findings of typical coved, down-sloping ST-segment elevation of at least 2 mm in the right precodial leads (V1-3).[15]

Statistical Analysis

Simple comparisons between patients diagnosed with true-positive and false-positive activations were performed with χ^2 test for categorical or binary data. For normally and non-normally distributed continuous data, the t-tests and Wilcoxon rank sum tests were used respectively. For univariate and multivariate analysis, logistic regression was used with the primary outcome variable of a false-positive activation.

The statistical output is reported as an odds ratio (OR) and 95% confidence interval. Non-normally distributed variables are presented as median values and interquartile range while continuous variables are presented as means and standard deviations. A P value <0.05 is considered statistically significant.

All statistical analysis were performed using SPSS version 20.0

Results

A total of 1864 patients were identified from the CVL records in the study period, of which, 55 patients were excluded from the study (Fig. 1). These patients were excluded for the following reasons: CVL was activated from locations other than the ED, CVL was activated during the blanking period and aborted/incomplete coronary angiograms.

In total, 1809 patients were included in the study. Among these, 84 (4.6%) were identified as false-positives. The incidence of false-positives before and after implementation of direct CVL activation was 4.1% and 5.1% respectively, which was not statistically significant (P = 0.315).

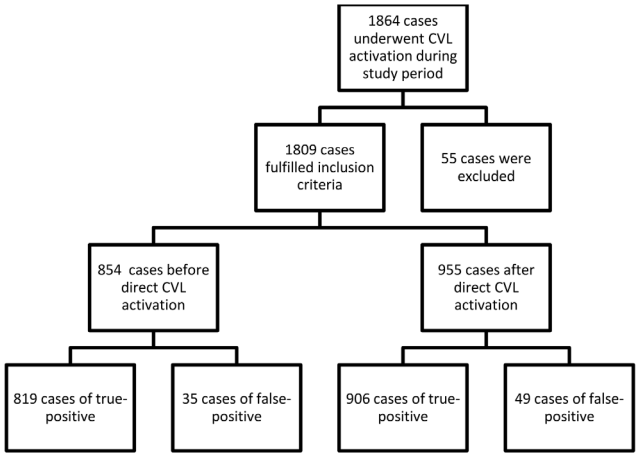

Fig. 1. Number of patients screened and the eventual study population.

Tables 1 and 2 show the univariate analysis of the patient's demographics, cardiovascular risk factors, previous cardiac history (including previous MI, previous coronary angioplasty or coronary artery bypass graft [CABG]), and clinical presentations. Female gender, non-smoker, absence of chest pain upon presentation at ED and presence of only left bundle branch block (LBBB) in ECG were associated with increased rates of false-positive CVL activation.

Table 1. Baseline Characteristics Comparison between True- and False-Positive STEMI Activation

Demographics	True-Positive (n = 1725)	False-Positive (n = 84)	*P* Value
Age, mean (SD), years	58.5 (11.5)	59.0 (12.6)	0.744
Female sex, no (%)	285 (16.5)	27 (32.1)	0.001
Race			
Chinese (%)	1103 (63.9)	60 (71.4)	0.199
Malay (%)	251 (14.5)	7 (8.3)	0.148
Indian (%)	281 (16.2)	11 (13.0)	0.543
Cardiovascular risk factors			
Non-smoker (%)	965 (55.9)	67 (79.7)	<0.005
Hypertension (%)	971 (56.3)	41 (48.8)	0.179
Diabetes (%)	530 (30.7)	21 (25.0)	0.331
Hyperlipidaemia (%)	914 (53%)	37 (44%)	0.118
Family history of CAD (%)	222 (12.8)	5 (5.9)	0.064
Previous cardiac history			
MI (%)	170 (9.8)	10 (11.9)	0.573
PCI (%)	254 (14.7)	14 (16.7)	0.637
CABG (%)	54 (3.1)	4 (4.8)	0.342

CABG: Coronary artery bypass graft; CAD: Coronary heart disease; MI: Myocardial infarction; PCI: Percutaneous coronary intervention

After multivariate logistic regression analysis, female gender (OR: 2.1 [1.2-3.5], $P = 0.005$), absence of chest pain (OR: 5.4 [3.0-9.5], $P < 0.001$) and presence of only LBBB (OR: 65.7 [19.9-217.2], $P < 0.001$) were independently associated with an increased odds of false-positive CVL activation.

In addition, we compared the clinical outcome of patients before and after implementation of direct CVL activation. There was no increase in mean length of stay, non-Killip 4 cardiac mortality and in lab complications between the 2 groups as shown in Table 3.

Final diagnoses of all 84 false-positive CVL activations are listed in Table 4. Common causes of false-positive activation in our study were early repolarisation ECG

Table 2. Clinical Factors Comparison between True-Positive and False-Positive STEMI Activation

Clinical Factors	True-Positive (n = 1725)	False-Positive (n = 84)	*P* Value
Indications for CVL activation			
Chest pain	1629 (94.4)	60 (71.4)	
Absence of chest pain (%)	96 (5.6)	24 (28.6)	0.001
Collapse	36 (2.0)	4 (4.7)	0.111
ECG changes	55 (3.1)	17 (20.2)	<0.001
Arrhythmias	2 (0.1)	2 (2.3)	0.012
Acute pulmonary oedema	3 (0.1)	0 (0)	1.000
After office hours presentation (%)	790 (45.8)	30 (35.7)	0.073
ECG localisation on presentation at ED			
Anterior (%)	806 (46.7)	35 (41.6)	0.373
Inferior (%)	787 (45.6)	16 (19.0)	0.000
Lateral only (%)	43 (2.5)	0 (0.0)	0.262
Posterior only (%)	6 (0.3)	0 (0.0)	1.000
LBBB only (%)	4 (0.2)	14 (16.7)	0.001

CVL: Cardiovascular laboratory; ECG: Electrocardiogram; ED: Emergency department; LBBB: Left bundle branch block

Table 3. Index Hospitalisation Outcomes Before and After Direct CVL Activation

Outcome	Before (n = 854)	After (n = 955)	*P* Value
Length of stay, mean, days	5.5	5.81	0.446
In lab complications (%)	98 (11.0)	37 (3.9)	<0.0001
Non-Killip 4 cardiac mortality (%)	16 (1.9)	17 (1.8)	1

CVL: Cardiovascular laboratory

Table 4. Breakdown of Causes of False-Positive CVL Activation in Our Series

Final Diagnosis	No. (n = 84)
Early repolarisation	23
Old myocardial infarction changes	14
Left bundle branch block	12
Perimyocarditis	8
Persistent chest pain with no ECG changes	7
Takotsubo cardiomyopathy	5
Pulmonary embolism	3
Subarachnoid haemorrhage	2
Ventricular tachycardia	2
Pulseless electrical activity	1
Brugada syndrome	1
Left ventricular hypertrophy	1
Coronary spasm	1
Others	4

CVL: Cardiovascular laboratory; ECG: Electrocardiogram

Table 5. Causes of False-Positive Activation in Female Gender

Causes	No. (n = 27)
Takotsubo cardiomyopathy	5 (18.5%)
Early repolarisation	5 (18.5%)
Myopericarditis	3 (11.1%)
Left bundle branch block	3 (11.1%)
Old myocardial infarction changes	3 (11.1%)
Subarachnoid haemorrhage	1 (3.7%)
Pulmonary embolism	1 (3.7%)
Others	6 (22.2%)

changes, old MI ECG pattern and presence of LBBB in ECG. We further stratified causes of false-positive activation according to female gender as shown in Table 5.

Discussion

In current literature, the reported false-positive AMI activation prevalence ranges from 9.5% to 36%.[16,17] Our series reported a 5.1% false-positive rate after the introduction of direct CVL activation which is seemingly lower than those reported. One possible explanation is the lack of a universal definition of what constitutes as false-positive activation. McCabe et al included cases without any cardiac catheterisation lacking in 2 out of 3 lines of evidence supporting a STEMI diagnosis as false-positive, potentially explaining their relatively higher rate of false-positive activation of 36%. On the other hand, Larson et al adopted a more nuanced approach by giving a range of false-positive activation rate ranging from 9.5% to 14% depending on the definition of false-positive activation adopted. Regardless, the purpose of direct CVL activation as espoused by the American Heart Association (AHA) is such that patients with suspected STEMI are able to undergo urgent angiography and reperfusion therapy within the 90 minutes time frame.[3] As such, our false-positive definition is based on absence of compelling angiographic findings that warrants reperfusion therapy which will impact the clinical outcome positively.

There were several factors associated with false-positive activation, one of them being the absence of chest pain on presentation. From our study, we found that cardiovascular collapse, arrhythmias and ECG changes were indication for direct CVL activation in such patients. Although these presentations may arise due to AMI, other conditions can account for them and as such, false-positivity is not surprising. Similarly, other studies have also reported varying percentages of false-positive activation in the absence of chest pain on presentation, ranging from 17.9% to 33%.[16,18] However, 80% of all patients without chest pain on presentation had an acutely occluded culprit artery in our study. In light of higher prevalence of false-positive CVL activation of patients without chest pain, evaluation should be done to identify high risk features such as haemodynamic instability, cardiogenic shock and life threatening arrhythmias as recommended by current guidelines for immediate invasive evaluation and institution of appropriate therapy or revascularisation, accepting potentially higher rates of false-positive activations in this high risk population.[19]

The European Society of Cardiology (ESC) recommends urgent coronary angiogram for patients with chest pain suggestive of MI presenting with new or presumed new onset LBBB. However, our study showed that presence of only LBBB in the ECG is an independent predictor of false-positive activation. Several studies have also corroborated our findings, with incidence of AMI in patients with both chest pain and only new or presumed new LBBB ranging from 12.2% to 33%.[20,21] On the other hand, patients with ECG showing pre-existing LBBB, Sgarbossa criteria, ie. ST elevation of at least 1 mm that is concordant with the QRS complex, or ST depression of at least 1 mm in leads V2 and V3 should be used to determine the presence of AMI.[22] In our study, of the 16 patients that had CVL activation based on the presence LBBB only on ECG, 14 (87.5%) had false-positive activations. Although we concur with guideline recommendations for CVL activation in appropriate patients with new LBBB and chest pain with acceptance of high false-positive activations, efforts should be made to determine if the LBBB changes were pre-existing and if so, Sgarbossa criteria be used to diagnose AMI to

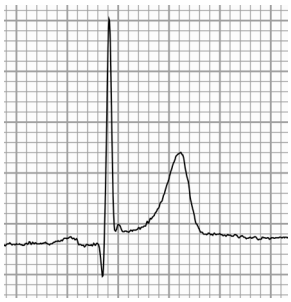

Fig. 2. Graph showing early repolarisation ECG changes.

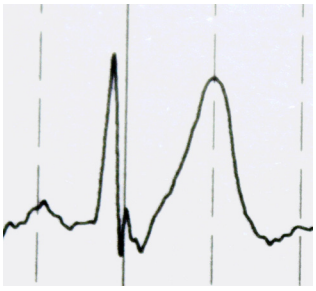

Fig. 3. Graph showing hyperacute T wave ECG changes.

reduce false-positive rates. The chronicity of LBBB at the time of presentation cannot be established for most patients because old ECGs are not available for comparison. Hence, given the heterogeneity of the causes of LBBB other than AMI, the 2013 American College of Cardiology (ACC)/AHA guidelines recommended that new or presumed new LBBB should not be considered diagnostic of AMI in isolation without other clinical presentations, e.g. chest pain, suggestive of AMI.

With regard to gender, females have a higher prevalence of false-positive activation in our study, with the commonest cause being Takotsubo stress cardiomyopathy, occurring exclusively in the females. Other studies have also reported increased prevalence of false-positives in the female gender.[16]

Contrary to previous studies,[16,17] our data did not show a significant increase in the risk of false-positives in patients with previously known MI, CABG or coronary artery disease. One possible explanation could be the slightly selective inclusion criteria for which these patients may not fulfill and as such may have had a cardiology consult at the ED to further stratify the patients for CVL activation.

Our study identified early repolarisation changes as the most common underlying cause for false-positive CVL activation accounting for 23 out of 84 false-positive activations (27%). This represents a common diagnostic dilemma in the ED which typically occurs in a young male patient occurring with chest pain. Characteristic early repolarisation ECG changes include a notch at the J point most prominently seen in V4, concave ST-segment elevation and tall asymmetrical T waves (Fig. 2).[23] This is in contrast to hyperacute ECG changes with MI where there is presence of sloped ST-segment elevation with loss of the normal ST concavity and tall symmetrical T waves (Fig. 3). If present, a previous ECG showing early repolarisation changes when the patient had no chest pain can help differentiate the ECG changes from AMI.

Limitations

Being a single centre study, we are unable to assume that our data is representative of patients with suspected STEMI presenting to ED around the world or even in Singapore for that matter. However, this is partially offset by factors such as the small size and predominantly urban setting of Singapore for which there is unlikely to be significant inter-hospital differences within Singapore.

Conclusion

In this series, we demonstrated that there was no significant increase in false activation rates through the introduction of direct CVL activation by emergency physicians. In addition, this emphasis on reduction of DTB time through such strategy did not result in worse clinical outcome. Factors associated with increased false-positive CVL activations especially the lack of chest pain or LBBB only should be taken into account with the clinical presentation when making a diagnosis of AMI. Larger studies or meta-analysis of similar studies are needed to confirm our findings and to derive a predictive model to accurately identify AMI patients who will benefit from CVL activations.

REFERENCES

1. Brodie BR, Hansen C, Stuckey TD, Richter S, Versteeq DS, Gupta N, et al. Door-to-balloon time with primary percutaneous coronary intervention for acute myocardial infarction impacts late cardiac mortality in high-risk patients and patients presenting early after the onset of symptoms. J Am Coll Cardiol 2006;47:289-95.
2. Rathore SS, Curtis JP, Chen J, Wang Y, Nallamothu BK, Epstein AJ, et al. Association of door-to-balloon time and mortality in patients admitted to hospital with ST elevation myocardial infarction: national cohort study. BMJ 2009;338:b1807.
3. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61;e78-140.
4. Khot UN, Johnson ML, Ramsey C, Khot MB, Todd R, Shaikh SR, et al. Emergency department physician activation of the catheterization laboratory and immediate transfer to an immediately available catheterization laboratory reduce door-to-balloon time in ST-elevation myocardial infarction. Circulation 2007;116:67-76.
5. Kontos MC, Kurz MC, Roberts CS, Joyner SE, Kreisa L, Omato JP, et al. Emergency physician-initiated cath lab activation reduces door to balloon times in ST-segment elevation myocardial infarction patients. Am J Emerg Med 2011;29:868-74.

6. Singer AJ, Shembekar A, Visram F, Schiller J, Russo V, Lawson W, et al. Emergency department activation of an interventional cardiology team reduces door-to-balloon times in ST-segment elevation myocardial infarction. Ann Emerg Med 2007;50:538-44.
7. Kraft PL, Newman S, Hanson D, Anderson W, Bastani A. Emergency physician discretion to activate the cardiac catheterization team decreases door-to balloon time for acute ST-elevation myocardial infarction. Ann Emerg Med 2007;50:520-6.
8. Krumholz HM, Bradley EH, Nallamothu BK, Ting HH, Batchelor WB, Kline-Rogers E, et al. A campaign to improve the timeliness of primary percutaneous coronary intervention: Door-to-Balloon: An Alliance Quality. JACC Cardiovasc Interv 2008;1:97-104.
9. Bradley EH, Herrin J, Wang Y, Barton BA, Webster TR, Mattera JA, et al. Strategies for reducing the door-to-balloon time in acute myocardial infarction. N Engl J Med 2006;355:2308-20.
10. Barbagelata A, Ware DL. Denying reperfusion or falsely declaring emergency: the dilemma posed by ST-segment elevation. J Electrocardiol 2006;39:S73-4.
11. Ong ME, Wong AS, Chan KP, Bergin AR, Sultana P, Lim SH, et al. Improving door-to-balloon times in Asia for acute ST elevation myocardial infarction via direct activation by emergency physicians of percutaneous coronary intervention. Int J Cardio 2010;145;613-4.
12. Mehta M, Jain AC, Mehta A. Early repolarization. Clin Cardiol 1999;22:59-65.
13. Klatsky AL, Oehm R, Cooper RA, Udaltsova N, Armstrong MA. The early repolarization normal variant electrocardiogram: correlates and consequences. Am J Med 2003;15:171-7.
14. Sharkey SW, Lesser JR, Zenovich AG, Maron MS, Lindberg J, Tonge TF, et al. Acute and reversible cardiomyopathy provoked by stress in women from the United States. Circulation 2005;111:472-9.
15. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, et al. Brugada syndrome: report of the second consensus conference. Circulation 2005;111:659-70.
16. McCabe JM, Armstrong EJ, Kulkarni A, Hoffmayer KS, Bhave PD, Garg S, et al. Prevalence and factors associated with false-positive ST-segment elevation myocardial infarction diagnoses at primary percutaneous coronary intervention-capable centers: a report from the Activate-SF registry. Arch Intern Med 2012;172:864-71.
17. Larson DM, Menssen KM, Sharkey SW, Duval S, Schwartz RS, Harris J, et al. "False-positive" cardiac catheterization laboratory activation among patients with suspected ST-segment elevation myocardial infarction. JAMA 2007;298:2754-60.
18. Bae MH, Cheon SS, Song JH, Jang SY, Choi WS, Kim KH, et al. Etiologies and predictors of ST-segment elevation myocardial infarction. Korean Circ J 2013;43:370-6.
19. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2014;35:2541-619.
20. Mozid AM, Mannakkara NN, Robinson NM, Jagathesan R, Sayer JW, Aggarwal RK, et al. Comparison of clinical characteristics and outcomes in patients with left bundle branch block versus ST-elevation myocardial infarction referred for primary percutaneous coronary intervention. Coron Artery Dis 2015;26:17-21.
21. Jain S, Ting HT, Bell M, Bjerke CM, Lennon RJ, Gersh BJ, et al. Utility of left bundle branch block as a diagnostic criterion for acute myocardial infarction. Am J Cardiol 2011;107:111-6.
22. Neeland IJ, Kontos MC, de Lemos JA. Evolving considerations in the management of patients with left bundle branch block and suspected myocardial infarction. J Am Coll Cardiol 2012;60:96-105.
23. Wang K, Asinger RW, Marriott HJ. ST-segment elevations in conditions other than acute myocardial infarction. N Engl J Med 2003;349:2128-35.

Original Article

Focal Nodular Hashimoto's Thyroiditis: Comparison of Ultrasonographic Features with Malignant and Other Benign Nodules

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Abstract

Introduction: Hashimoto's thyroiditis (HT) can present as focal nodular disease. This study aimed to determine the distinguishing sonographic features of nodules in biopsy-proven focal HT. Materials and Methods: The study included 388 thyroid nodules from 310 patients who underwent ultrasound-guided fine-needle aspiration biopsy (FNAB). There were 28 focal HT, 27 malignant and 333 other benign nodules. Sonographic features of focal HT nodules on prebiopsy ultrasound were compared with malignant nodules and other benign nodules using multinomial logistic regression adjusting for the correlation between multiple nodules obtained from the same patient. Results: Most focal HT nodules were purely solid (92.8%), iso-hyperechoic (70.4%), had regular margins (75.0%) and central vascularity (85.7%). Hypoechogenicity (29.6% vs 42.3%; *P* = 0.017) and microcalcifications (3.6% vs 44.4%; *P* = 0.003) were significantly less common in focal HT than malignant nodules. None of the focal HT nodules demonstrated marked hypoechogenicity, irregular margins or cervical lymphadenopathy, which are traditionally associated with malignancy. Compared to other benign nodules, focal HT nodules were significantly more likely to be purely solid (92.8% vs 49.0%; *P* = 0.016), ill-defined (25.0% vs 7.0%; *P* = 0.004) and lack comet-tail artefacts (92.9% vs 66.1%; *P* = 0.012), which in combination were 17.9% sensitive and 94.6% specific for focal HT. Conclusion: Awareness of the above-described sonographic appearances of focal HT may aid in differentiating them from malignant nodules and risk-stratify for FNAB. While there is substantial overlap with other benign nodules, a combination of the above-mentioned 3 ultrasound features is highly specific for focal HT and can prompt further serological evaluation in clinically unsuspected HT.

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Key words: FNAB, Ultrasound-guided thyroid biopsy

Introduction

Hashimoto's thyroiditis (HT), or chronic lymphocytic thyroiditis, is the most common cause of hypothyroidism in non-iodine-deficient countries.[1] The diagnosis is usually based on clinical and serological (serum antibodies against thyroid peroxidase and thyroglobulin) findings, with a limited role for ultrasound imaging.[2,3] Diffuse or patchy decrease in echogenicity, heterogeneous echotexture with micronodule formation, parenchymal hypervascularity and diffuse gland enlargement are the usual sonographic findings in HT.[4,5] Other than these diffuse patterns of involvement, HT may also present with nodular (often palpable) disease, with or without background parenchymal changes on ultrasound. This has been variably called focal or nodular HT.[4,5] These nodules can coexist with benign hyperplastic nodules as well as with malignancy, with an increased rate of lymphoma and papillary carcinoma reported in patients with HT.[3,6-8] Fine-needle aspiration biopsy (FNAB) is the most practical way of differentiating these entities. Meanwhile, it is not unusual for the initial diagnosis of HT to be made only after a biopsy of a thyroid nodule, suggesting a higher incidence of HT in the community than that detected from

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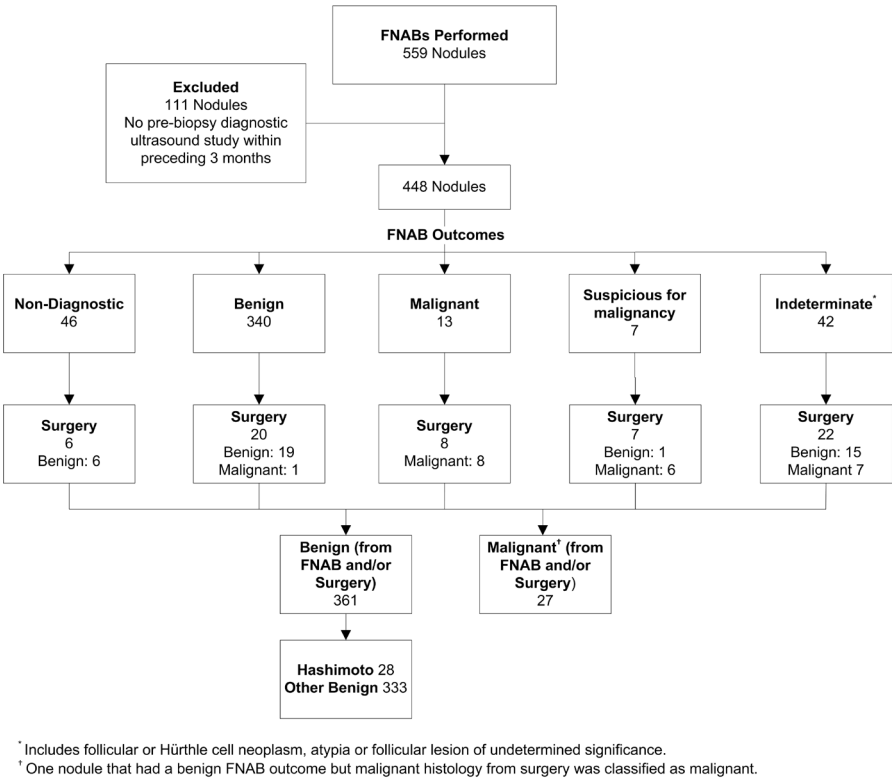

* Includes follicular or Hürthle cell neoplasm, atypia or follicular lesion of undetermined significance.
† One nodule that had a benign FNAB outcome but malignant histology from surgery was classified as malignant.

Fig. 1. Distribution of different types of thyroid nodules in the study sample.

clinical evaluation and biochemistry.[9,10] By directing the selection of nodules for FNAB, ultrasound can play a vital role in the surveillance for malignancy as well as in the potential early diagnosis of HT. However, currently there is limited data on the sonographic features of focal HT, with varying results on the features that distinguish them from malignant or other benign nodules.[4,5,11-14] To our knowledge, there is no previous study from Singapore that has assessed the ultrasound features of focal HT in the local population.

In 559 thyroid nodules that underwent ultrasound-guided FNAB, we found that well-defined irregular margins, microcalcifications, coarse calcifications and cervical lymphadenopathy were independent sonographic predictors of malignancy, and the use of a combination of these features can help to risk-stratify nodules for FNAB with high sensitivity and specificity of 81.5% and 93.1%, respectively.[15] The current study, based on the same patient cohort, aimed to describe the sonographic findings of biopsy-proven focal HT and identify features that can differentiate them from malignant or other benign nodules.

Materials and Methods

The study was performed with approval from the institutional review board. Between January 2010 and April 2013, a total of 559 ultrasound-guided thyroid nodule FNABs were performed in the radiology department of a tertiary institution. Thyroid nodules with a tissue diagnosis (from FNAB or surgical pathology, if available) and a diagnostic ultrasound within 3 months preceding the biopsy were included in this study. Thus, the final analysis was based on 388 nodules in 310 patients (60 males, 250 females; age range, 13 to 83 years; mean age: 53 years ± 14 SD) (Fig. 1). There were 28 (7.2%) nodules with focal HT (from 24 patients), 27 (7.0%) malignant nodules (from 19 patients) and 333 (85.8%) other benign nodules (from 273 patients). Of the malignant nodules, 23 were papillary carcinomas, 2 were medullary carcinomas and 2 were lymphomas. Of the other benign nodules, 321 were hyperplastic nodules and 12 were follicular adenomas. The overall prevalence of HT in this study population based on ultrasound-guided FNAB was 7.7% (24 of 310 patients).

The FNABs were performed using a 23-25G needle under sonographic guidance in the interventional radiology suite. There was an on-site cytotechnologist available to assess the adequacy of the biopsy samples. Histological results were used in lieu of cytology if the nodule underwent subsequent surgical resection. Relevant clinical (history of HT and thyroid hormone replacement) and biochemical (thyroid profile and thyroid antibody levels) information were also retrieved from the electronic medical records.

Images of diagnostic ultrasound studies performed within 3 months preceding the FNAB were retrospectively reviewed by an attending radiologist blinded to the FNAB and histological outcomes. The thyroid nodules were assessed for the following sonographic features: size (in the longest dimension); multiplicity; consistency (purely solid, predominantly [≥50%] solid, predominantly cystic and purely cystic); echogenicity of the solid component (with reference to the thyroid parenchyma and strap muscles); margins (well-defined regular, well-defined irregular [microlobulated or speculated] and ill-defined); the presence of a hypoechoic halo; colloid (tiny echogenic foci with comet-tail artefacts); a taller-than-wide shape (anteroposterior diameter more than transverse diameter on a transverse or longitudinal plane); central vascularity; and calcifications (rim, coarse or microcalcification). Thyroid gland enlargement and background parenchymal changes of diffuse HT (reduced echogenicity equal to or lower than that of the strap muscles, and heterogeneous echotexture with micronodule formation and hypervascularity) were also sought.

Data Analysis

Statistical analyses were performed on a per nodule basis using the STATA software (version 13.0; StataCorp, College Station, Texas, USA), assuming a two-sided test with conventional significance level of 0.05. The demographic and sonographic features of focal HT were compared with those of malignant nodules and other benign nodules using multinomial logistic regression, adjusting for the correlation between multiple nodules obtained from the same patient using a clustered robust variance estimation approach by considering both variability between patients and within the same patient (at the nodule level) in the parameter estimation.

Results

Clinical and Biochemical Profile of Patients with Focal HT

Ten patients (with 12 nodules) with biopsy-proven focal HT had a known prebiopsy diagnosis of HT, of which 8 were on thyroid hormone replacement and 2 were euthyroid at the time of biopsy. Meanwhile, the remaining 14 patients (16 nodules) had their first diagnosis of HT made on ultrasound-guided FNAB. Most of them were euthyroid with only 1 hypothyroid (elevated thyrotropin [TSH] and low free thyroxine [T4] levels) patient. Antithyroglobulin and antithyroid peroxidase antibody titres were available in 19 of the 24 patients and were elevated in 16 of them (84.2%).

Background Ultrasound Features of HT

All patients with biopsy-proven focal HT had diffuse heterogeneity of the parenchymal echotexture, while 14 (58.3%) of them had the typical appearance of diffuse HT (micronodule formation, reduced parenchymal echogenicity equal to or lower than that of the strap muscles and increased vascularity) (Fig. 2). Twenty-one patients (87.5%) had an enlarged thyroid gland (anteroposterior diameter more than 18 mm)[16] at ultrasound, while the rest had a normal-sized thyroid gland.

Demographic Information and Sonographic Features of Nodules in Focal HT and Comparison with Malignant and Other Benign Nodules

Among the 24 patients with HT, 23 (95.8%) of them were female. The mean age was 46 years ± 15 (SD) (range, 18 to 82 years). There was no significant difference in age and gender between patients with focal HT, malignant nodules or other benign nodules (Table 1).

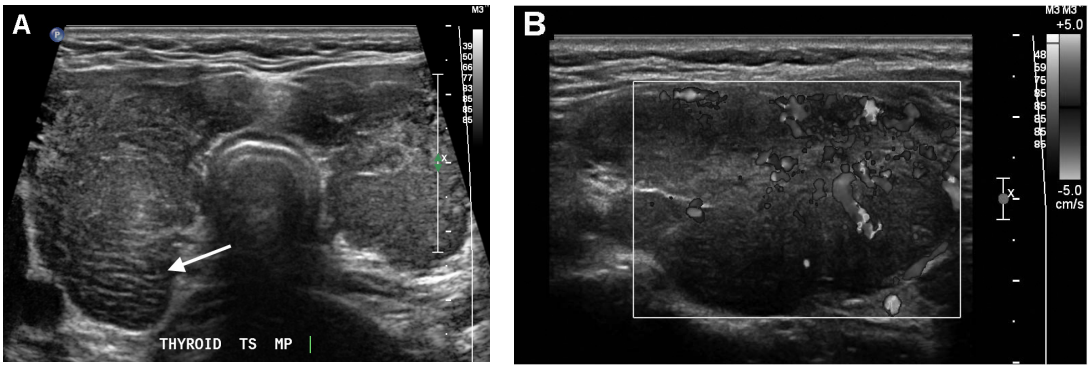

Fig. 2. A) is a transverse greyscale image of the thyroid gland from a 44-year-old woman referred for a diffuse goitre. There was no known history of HT. The thyroid gland shows diffuse asymmetrical enlargement (right lobe more than left). There are features of diffuse HT in the background parenchyma—heterogeneous echotexture with micronodule formation (arrow) and geographic areas of hypoechogenicity (comparable to that of the strap muscles). However, no discrete focal nodule is otherwise seen in this cross section. B) is a colour Doppler image of the left thyroid lobe demonstrating increased parenchymal vascularity, another feature of diffuse HT.

Table 1. Demographic and Sonographic Features of Focal HT, Malignant and Other Benign Nodules

	Nodules			Focal HT vs Malignant		Focal HT vs Other Benign	
	Focal HT (n = 28)	**Malignant (n = 27)**	**Other Benign (n = 333)**	**Crude RRR* (95% CI)**	***P* Value***	**Crude RRR* (95% CI)**	***P* Value***
Age, mean ± SD	49 ± 16	48 ± 16	55 ± 14	1.00 (0.95 to 1.05)	0.947	0.97 (0.94 to 1.00)	0.081
Female gender, no. (%) of patients	27 (96.4)	22 (81.5)	270 (81.1)	6.14 (0.56 to 66.98)	0.137	6.30 (0.83 to 48.09)	0.076
Size of nodule in mm, mean ± SD	19 ± 13	17 ± 13	24 ± 12	1.02 (0.94 to 1.11)	0.605	0.95 (0.90 to 1.01)	0.106
Internal content, no. (%)							
Purely cystic or predominantly cystic	1 (3.6)	1 (3.7)	77 (23.1)	1.00 (reference)	-	1.00 (reference)	-
Purely solid	26 (92.8)	25 (92.6)	163 (49.0)	1.04 (0.06 to 18.13)	0.979	12.29 (1.59 to 95.03)	0.016
Predominantly solid	1 (3.6)	1 (3.7)	63 (18.9)	1.00 (0.02 to 50.74)	1.000	1.22 (0.07 to 20.06)	0.888
Spongiform†	0 (0.0)	0 (0.0)	30 (9.0)	-	-	-	-
Taller-than-wide shape, no. (%)	2 (7.1)	6 (22.2)	18 (5.4)	0.27 (0.03 to 2.36)	0.236	1.35 (0.17 to 10.59)	0.778
Margins, no. (%)							
Well-defined regular	21 (75.0)	7 (25.9)	300 (90.1)	1.00 (reference)	-	1.00 (reference)	-
Well-defined irregular (microlobulated or spiculated)	0 (0.0)	16 (59.3)	8 (2.4)	-	-	-	-
Ill-defined	7 (25.0)	4 (14.8)	25 (7.5)	0.58 (0.13 to 2.69)	0.490	4.00 (1.57 to 10.16)	0.004
Echogenicity of solid component,§ no. (%)							
Isoechoic	15 (55.6)	3 (11.5)	169 (57.1)	1.00 (reference)	-	1.00 (reference)	-
Hypoechoic	8 (29.6)	11 (42.3)	85 (28.7)	0.15 (0.03 to 0.71)	0.017	1.06 (0.43 to 2.62)	0.899
Markedly hypoechoic	0 (0.0)	10 (38.5)	5 (1.7)	-	-	-	-
Hyperechoic	4 (14.8)	2 (7.7)	37 (12.5)	0.40 (0.05 to 3.24)	0.391	1.22 (0.39 to 3.80)	0.734
Solitary nodule, no. (%)	2 (7.1)	4 (14.8)	28 (8.4)	0.44 (0.05 to 3.94)	0.465	0.84 (0.18 to 3.80)	0.891
Hypoechoic halo‖, no. (%)	13 (52.0)	3 (12.0)	175 (69.2)	7.94 (1.95 to 32.34)	0.004	0.48 (0.22 to 1.04)	0.063
Calcifications, no. (%)							
No calcification	25 (89.2)	12 (44.4)	315 (94.6)	1.00 (reference)	-	1.00 (reference)	-
Microcalcifications	1 (3.6)	12 (44.4)	3 (0.9)	0.04 (0.005 to 0.33)	0.003	4.20 (0.44 to 39.64)	0.211
Rim calcifications	1 (3.6)	0 (0.0)	3 (0.9)	-	-	4.20 (0.42 to 42.24)	0.223
Coarse calcifications	1 (3.6)	3 (11.2)	12 (3.6)	0.16 (0.01 to 1.76)	0.134	1.05 (0.13 to 8.80)	0.964
Comet-tail artefacts,§ no. (%)	2 (7.1)	1 (3.9)	113 (33.9)	1.92 (0.16 to 23.38)	0.608	0.15 (0.03 to 0.66)	0.012
Central vascularity,§ no. (%)	24 (85.7)	19 (73.1)	235 (70.6)	2.21 (0.60 to 8.18)	0.235	2.50 (0.85 to 7.33)	0.094
Cervical lymphadenopathy¶ no. (%)	0 (0.0)	5 (18.5)	0 (0.0)	-	-	-	-

HT: Hashimoto's thyroiditis; RRR: Relative risk ratio; SD: Standard deviation

*Obtained using multinomial logistic regression accounting for the correlation between multiple nodules obtained from the same patient.

†No further analysis performed as spongiform consistency was only seen in other benign nodules.

‡Excluding purely cystic nodules.

§There were diffuse coarse calcifications in one malignant nodule, which prevented further assessment of echogenicity, vascularity and for presence of comet tail artefacts.

‖Excluding purely cystic or predominantly cystic nodules.

¶No further analysis performed as cervical lymphadenopathy was only seen in malignant nodules.

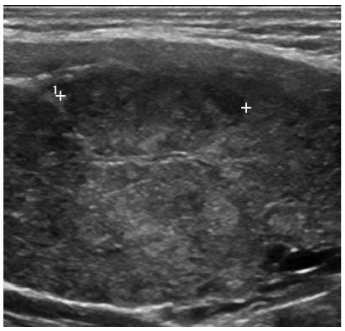

Fig. 3. Longitudinal greyscale image of cytology-proven focal HT from a 30-year-old woman with diffuse goitre. There was no known history of HT. The nodule (marked by cursors) is purely solid with ill-defined margins, isoechoic and lacks internal colloid (tiny echogenic foci with posterior comet-tail artefacts). The background parenchyma demonstrates features of diffuse HT.

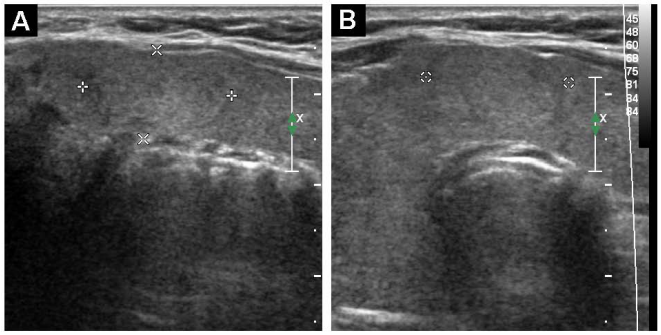

Fig. 4. A) Longitudinal greyscale image of cytology-proven focal HT from a 52-year-old woman with diffuse goitre. There was no known history of HT. The nodule (marked by cursors) is purely solid with ill-defined margins, isoechoic to the background parenchyma and lacks comet-tail artefacts. The background parenchyma is unremarkable except for subtle heterogeneity. B) Transverse greyscale image of the same nodule (marked by cursors).

Nodules in focal HT were most often purely solid (92.8%) with well-defined regular margins (75.0%) and isoechoic to the thyroid parenchyma (55.6%). A substantial minority (25.0%) had ill-defined margins (Figs. 3 and 4). Most of the nodules demonstrated central vascularity (85.7%). A hypoechoic halo was present in almost half the nodules. Colloid (comet-tail artefacts) (7.1%), a taller-than-wide shape (7.1%) and calcifications of any kind (10.8%) were infrequently seen (Table 1).

Nodules in focal HT were significantly less likely than malignant nodules to be hypoechoic (29.6% vs 42.3%; crude relative risk ratio [CRRR] = 0.15; 95% CI, 0.03 to 0.71; $P = 0.017$) or contain microcalcifications (3.6% vs 44.4%; CRRR = 0.04; 95% CI, 0.005 to 0.33; $P = 0.003$), and were more likely to have a hypoechoic halo (52.0% vs 12.0%; CRRR = 7.94; 95% CI, 1.95 to 32.34; $P = 0.004$) (Table 1). Well-defined irregular (microlobulated or spiculated) margins, marked hypoechogenicity and cervical lymphadenopathy were not seen in any nodule with focal HT but were present in 59.3%, 38.5% and 18.5% of malignant nodules, respectively.

Compared to other benign nodules, focal HT rarely had comet-tail artefacts on ultrasound (7.1% vs 33.9%; CRRR = 0.15; 95% CI, 0.03 to 0.66; $P = 0.012$). Meanwhile, they were significantly more likely to have ill-defined margins (25.0% vs 7.5%; CRRR = 4.00; 95% CI, 1.57 to 10.16; $P = 0.004$) and purely solid consistency (92.8% vs 49.0%; CRRR = 12.29; 95% CI, 1.59 to 95.03; $P = 0.016$) (Table 1).

There were 5 nodules (17.9%) with focal HT that displayed a combination of the 3 sonographic features of purely solid consistency, ill-defined margins and absence of colloid. This combination was rarely seen in other benign nodules (18 nodules; 5.4%). Using the coexistence of these 3 sonographic features as an indicator of focal HT, the diagnostic sensitivity and specificity were 17.9% and 94.6%, respectively. Four of these nodules were from patients in whom FNAB led to the initial diagnosis of HT.

Discussion

On FNAB, HT demonstrates follicular atrophy, metaplastic Hürthle cells and diffuse lymphocytic infiltration in close association with follicular cells and varying degrees of fibrosis.[2,5,17] The prevalence of HT based on ultrasound-guided FNAB in our study population was 7.7%, within the range (4% to 13.4%) quoted in previous FNAB-based studies[4,5,10,18] and much higher than the reported clinical prevalence of HT (0.5% to 0.8 %).[10] Staii et al rationalised this discrepancy with the intuitive argument that cytological diagnosis would always precede clinical diagnosis.[10] We believe that the element of selection bias may also account for the higher frequency of HT in cytology-based series.

The nodules in focal HT have been described on ultrasound as hypoechoic with ill-defined margins by Takashima et al,[13] solid and hyperechoic with ill-defined margins by Langer et al,[4] and solid and hypoechoic with a substantial minority (40%) possessing ill-defined margins by Anderson et al.[5] In our study, most of the focal HT nodules were solid (92.8%) and iso-hyperechoic (70.4%) with well-defined regular margins (75.0%) and central vascularity (85.7%). Diffuse heterogeneity of the background parenchyma (100%) and enlargement of the gland (87.5%) were also frequently encountered, although the typical micronodular parenchymal pattern was seen in less than 60% of our patients. Once again, this may be attributed to cytology permitting early diagnosis, which is also indicated by the euthyroid status of the majority of our patients.

The association between HT and papillary thyroid carcinoma has been widely described, with frequency of cancer between 10% to 58% on surgical pathology

series.[7,8,12,19] The risk of thyroid lymphoma, while still very low overall, has also been reported to be up to 80 times higher in the presence of HT.[3,6] It has therefore been recommended that FNAB be performed in patients with HT and a suspicious nodule.[1,3] The role of ultrasound in selecting discrete thyroid nodules for biopsy in patients with HT is unclear. Some studies recommend risk stratification using ultrasound, based on previously published sonographic criteria for malignancy,[11,12,20] while others have failed to demonstrate specific features that can differentiate focal HT from malignancy.[4,13] Overall, our results are broadly in agreement with the former thought. Previously described sonographic features of malignancy such as hypoechogenicity, marked hypoechogenicity, irregular margins, microcalcifications and cervical lymphadenopathy are significantly more common in malignancy than focal HT. Meanwhile, other features associated with malignant nodules, such as a taller-than-wide shape and coarse calcifications were not useful in differentiating them from focal HT. This may be due to the increased fibrosis in focal HT nodules, leading to a harder consistency and decreased compressibility with a resultant taller-than-wide shape.[21] Increased fibrosis may also account for dystrophic calcifications manifesting as coarse calcification on ultrasound.[22] Central vascularity was almost equally frequent in both focal HT and malignant nodules (85.7% vs 73.1%). This may be attributed to the increased sensitivity of modern high quality scanners in detecting even mild degrees of internal vascularity in solid nodules.[22]

Few studies have directly compared sonographic features of cytology-confirmed focal HT with those of other benign nodules. Anderson et al[11] found focal HT to be more likely solid, isoechoic, avascular and ill-defined. Fu et al found most nodules in focal HT to be hypovascular, although some of them had a specific hypervascularity that they termed 'focal thyroid inferno' (vascularity throughout the entire nodule).[14] We found considerable overlap in the sonographic features of focal HT and other benign nodules, although a few interesting observations were made. Almost all the nodules in focal HT (92.8%) were purely solid, compared to less than half (49.0%) of the other benign nodules. This can be explained by considering the natural history of hyperplastic nodules in multinodular goitre, whereby cycles of exacerbation and remission have led to haemorrhage and cystic degeneration, forming cystic spaces filled with blood product and colloid.[23] The same concept also explains the rarity of comet-tail artefacts in focal HT (7.1% vs 33.9 %), since this phenomenon is a signature of colloid within a thyroid nodule.[22] A quarter of nodules in focal HT also had ill-defined margins, which were rarely seen in other benign nodules (7.5%). In HT, this may be due to heterogeneous background echotexture secondary to diffuse or focal inflammatory infiltration.

In our study, more than half of the patients with HT had their initial diagnosis made on ultrasound-guided FNAB. In an attempt to recognise a diagnostic imaging pattern for focal HT in relation to other benign nodules, we found that a combination of 3 greyscale sonographic characteristics (namely, purely solid consistency, ill-defined margins and absence of comet-tail artefacts) was almost 95% specific for focal HT. When present on ultrasound, these features can prompt further serological evaluation for HT in clinically unsuspected cases. This may be especially useful when there are no background parenchymal features of HT. An early diagnosis of HT may be particularly valuable in women of child-bearing age, since maternal thyroid status has a major impact on the fetal outcome as well as on the well-being of the newborn.[24] However, the usefulness of this combination of sonographic features is limited by its low sensitivity (17.9%).

There are limitations to our study. There is selection bias as the nodules in our study population have been referred for FNAB only after diagnostic ultrasound, and may have been assessed to be of a higher risk of malignancy from clinical history or imaging features. A relatively small number of focal HT and malignant nodules have been compared with a large number of other benign nodules. However, it may be argued that this reflects the practical clinical scenario. The ultrasound images were assessed by a single radiologist. Nevertheless, previous studies have reported fair to substantial interobserver agreement for the assessment of greyscale and Doppler sonographic features.[25-27] We relied on cytological outcomes instead of surgical pathology to assign most of the diagnoses. However, the high diagnostic accuracy of thyroid nodule FNAB is well-acknowledged.[28]

Conclusion

Most focal HT nodules are purely solid and iso-hyperechoic with well-defined margins and central vascularity. Previously described sonographic criteria for malignancy remain useful in distinguishing malignant nodules from focal HT and can be used to risk-stratify nodules for FNAB in the ultrasound follow-up of HT. However, some features associated with a malignant nodule (namely, a taller-than-wide shape, coarse calcifications and central vascularity) may be less useful. While there is substantial overlap in sonographic features with other benign nodules, a combination of purely solid consistency, ill-defined margins and absence of comet-tail artefacts is highly specific for focal HT. This can prompt further serological evaluation and possible early diagnosis of clinically unsuspected HT, although its value is limited by low sensitivity.

REFERENCES

1. Pearce EN, Farwell AP, Braverman LE. Thyroiditis. N Engl J Med 2003;348:2646-55.
2. Caturegli P, De Remigis A, Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. Autoimmun Rev 2014;13:391-7.
3. Dayan CM, Daniels GH. Chronic autoimmune thyroiditis. N Engl J Med 1996;335:99-107.
4. Langer JE, Khan A, Nisenbaum HL, Baloch ZW, Horii SC, Coleman BG, et al. Sonographic appearance of focal thyroiditis. AJR Am J Roentgenol 2001;176:751-4.
5. Anderson L, Middleton WD, Teefey SA, Reading CC, Langer JE, Desser T, et al. Hashimoto thyroiditis: Part 1, sonographic analysis of the nodular form of Hashimoto thyroiditis. AJR Am J Roentgenol 2010;195:208-15.
6. Holm LE, Blomgren H, Lowhagen T. Cancer risks in patients with chronic lymphocytic thyroiditis. N Engl J Med 1985;312:601-4.
7. Cipolla C, Sandonato L, Graceffa G, Fricano S, Torcivia A, Vieni S, et al. Hashimoto thyroiditis coexistent with papillary thyroid carcinoma. Am Surg 2005;71:874-8.
8. Caturegli P, De Remigis A, Chuang K, Dembele M, Iwama A, Iwama S. Hashimoto's thyroiditis: celebrating the centennial through the lens of the Johns Hopkins hospital surgical pathology records. Thyroid 2013;23:142-50.
9. Poropatich C, Marcus D, Oertel YC. Hashimoto's thyroiditis: fine-needle aspirations of 50 asymptomatic cases. Diagn Cytopathol 1994;11:141-5.
10. Staii A, Mirocha S, Todorova-Koteva K, Glinberg S, Jaume JC. Hashimoto thyroiditis is more frequent than expected when diagnosed by cytology which uncovers a pre-clinical state. Thyroid Res 2010;3:11.
11. Anderson L, Middleton WD, Teefey SA, Reading CC, Langer JE, Desser T, et al. Hashimoto thyroiditis: Part 2, sonographic analysis of benign and malignant nodules in patients with diffuse Hashimoto thyroiditis. AJR Am J Roentgenol 2010;195:216-22.
12. Gul K, Dirikoc A, Kiyak G, Ersoy PE, Ugras NS, Ersoy R, et al. The association between thyroid carcinoma and Hashimoto's thyroiditis: the ultrasonographic and histopathologic characteristics of malignant nodules. Thyroid 2010;20:873-8.
13. Takashima S, Matsuzuka F, Nagareda T, Tomiyama N, Kozuka T. Thyroid nodules associated with Hashimoto thyroiditis: assessment with US. Radiology 1992;185:125-30.
14. Fu X, Guo L, Zhang H, Ran W, Fu P, Li Z, et al. "Focal thyroid inferno" on color Doppler ultrasonography: a specific feature of focal Hashimoto's thyroiditis. Eur J Radiol 2012;81:3319-25.
15. Zhang J, Chen Z, Anil G. Ultrasound-guided thyroid nodule biopsy: outcomes and correlation with imaging features. Clin Imaging 2015;39:200-6.
16. Rumack CM. Diagnostic ultrasound. 4th ed. Elsevier/Mosby: Philadelphia, PA; 2011. p. 708-49.
17. Baloch ZW, LiVolsi VA, Asa SL, Rosai J, Merino MJ, Randolph G, et al. Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: a synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. Diagn Cytopathol 2008;36:425-37.
18. Lin JD, Huang BY, Weng HF, Jeng LB, Hsueh C. Thyroid ultrasonography with fine-needle aspiration cytology for the diagnosis of thyroid cancer. J Clin Ultrasound 1997;25:111-8.
19. Paparodis R, Imam S, Todorova-Koteva K, Staii A, Jaume JC. Hashimoto's thyroiditis pathology and risk for thyroid cancer. Thyroid 2014;24:1107-14.
20. Moon HJ, Kim EK, Kim MJ, Kwak JY. Lymphocytic thyroiditis on fine-needle aspiration biopsy of focal thyroid nodules: approach to management. AJR Am J Roentgenol 2009;193:W345-9.
21. Yoon SJ, Yoon DY, Chang SK, Seo YL, Yun EJ, Choi CS, et al. "Taller-than-wide sign" of thyroid malignancy: comparison between ultrasound and CT. AJR Am J Roentgenol 2010;194:W420-4.
22. Anil G, Hegde A, Chong FH. Thyroid nodules: risk stratification for malignancy with ultrasound and guided biopsy. Cancer Imaging 2011;11:209-23.
23. Reading CC, Charboneau JW, Hay ID, Sebo TJ. Sonography of thyroid nodules: a "classic pattern" diagnostic approach. Ultrasound Q 2005;21:157-65.
24. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999;341:549-55.
25. Moon WJ, Jung SL, Lee JH, Na DG, Baek JH, Lee YH, et al. Benign and malignant thyroid nodules: US differentiation—multicenter retrospective study. Radiology 2008;247:762-70.
26. Choi SH, Kim EK, Kwak JY, Kim MJ, Son EJ. Interobserver and intraobserver variations in ultrasound assessment of thyroid nodules. Thyroid 2010;20:167-72.
27. Park CS, Kim SH, Jung SL, Kang BJ, Kim JY, Choi JJ, et al. Observer variability in the sonographic evaluation of thyroid nodules. J Clin Ultrasound 2010;38:287-93.
28. Gharib H. Current evaluation of thyroid nodules. Trends Endocrinol Metab 1994;5:365-9.

Use of Prediction Models for Risk Analysis and Decision-Making in Public Health—The Catch-22 Conundrum

Dear Editor,

Shirin Kalimuddin and colleagues presented a paper on "Dengue disease modelling and forecasting: utility and limitations" in the April 2016 edition of Annals. Referencing the joint media release by the National Environment Agency (NEA) and Ministry of Health (MOH) on 18 February 2016,[1] Kalimuddin et al discussed the limitations of models and forecasting as useful tools for eliciting a response to an impending outbreak. We believe the paper misrepresents some aspects of how dengue is controlled and managed in Singapore.

We agree that, as with many scientific methods, mathematical modelling has its limitations, and we welcome the authors particularly highlighting studies such as the Ebola models. However, readers would be wrong to conclude that mathematical modelling outputs should be dismissed. In particular, the authors did not mention the many successful modelling studies that have facilitated public health policies, such as the robust regression analysis method—least absolute shrinkage and selection operator (LASSO)—behind the Singapore dengue forecast.[2] As discussed in the published paper, because LASSO is built to optimise the accuracy of prediction by the forecast model, using separate sub-models for each forecast week shows little degradation in the quality of its long-term predictions. In fact, in the past years, we have accurately predicted the large dengue outbreaks of both 2013 and 2014, and the lull year of 2015. This was enabled by a good knowledge of the overall epidemiology of dengue in Singapore, to which modelling contributes. Yap and colleagues have described the comprehensive risk analysis, in addition to the model, performed by NEA that supported the prediction of a higher number of cases in 2016, in the media release.[3]

Based on NEA's surveillance and risk analysis programme, factors such as warmer temperature, increase in mosquito population and switch in serotype of circulating virus were taken into consideration together with output from the dengue model to arrive at the dengue forecast, as elaborated below. Briefly, the 2015 El Niño phenomenon is expected to drive up the dengue incidence on both the global and regional scale. The unusually high dengue incidence observed at the beginning of 2016 was likely due to the increase in temperature caused by this weather condition. Correlation analysis of the previous peak El Niño 3.4 sea surface temperature (SST) in 1997 showed a two-tiered delayed effect on dengue cases. The dengue incidence increased 1 to 2 months after the peak of El Niño 3.4 SST, and again 7 to 8 months later—leading to the well-known 1998 dengue pandemic that affected many countries globally. This was further supported by a collaborative study where researchers analysing dengue epidemics in Southeast Asia saw a synchronised increase in dengue incidence in this region in 1998, 1 year after the 1997 El Niño simultaneously heated up this large area.[4] The 2015 El Niño 3.4 SST peaked in December and has appeared to be just as strong as that observed in 1997, thus suggesting a poor dengue outlook in 2016.

At the same time, the *Aedes aegypti* mosquito population, from NEA's Gravitrap surveillance system, showed a persistent increase from the end of 2015 to the beginning of 2016. Compared to the same period in January 2015, 50% more *Aedes aegypti* mosquitoes were caught in Gravitraps deployed islandwide. The number of *Aedes aegypti* breeding in homes found during NEA's regular inspections in early 2016 was also 50% more than in the same period in January 2015. Furthermore, NEA's and MOH's virus surveillance had detected a switch in the predominant dengue serotype (from dengue virus type 1 [DENV-1] to dengue virus type 2 [DENV-2]) towards the end of 2015. In the last 10 years, it has been observed that a change in predominant dengue virus serotype has been followed by a spike in dengue cases.[5]

NEA's studies on blood donor samples from Singapore residents, in collaboration with the Health Sciences Authority of Singapore (HSA), have shown consistently low dengue herd immunity in our resident population. Dengue seroprevalence in young adults (16 to 30 years old) was low, with serotype-specific immunity of 13.4% for DENV-1 and 16.3% for DENV-2 in 2013. Thus, the Singapore resident population remains highly susceptible to dengue.

The warmer temperatures, increase in mosquito population and change in main circulating virus serotype, juxtaposed with low dengue herd immunity of Singaporeans, support the statistical projection of dengue cases in 2016. This model

has been a useful tool to support decision-making for NEA and has been continuously finetuned to incorporate more data as they become available.

Readers may erroneously assume that a pre-emptive response to a dengue outbreak involves only a surge capacity contributed by a "pool of readily available trained human resource in disease surveillance and control (that) could be activated at short notice". It is noteworthy to highlight that an effective dengue control programme involves the collective and coordinated effort of many stakeholders, including the community.[6] The article "Dengue is a community battle" in the media demonstrates such understanding, even in the lay community.[7] Besides public education and mobilisation, NEA leads an Inter-Agency Dengue Task Force (IADTF) comprising 25 stakeholders from the public, private and people (3P) sectors, to coordinate nationwide dengue control efforts. Temporal risk stratification through forecasting has allowed NEA and MOH to make a timely call for action among stakeholders through national campaigns and internal coordination.

A case in point is the media release "Dengue cases may exceed 30,000 in 2016" referenced by the authors.[6] In view of the potential risk of a severe dengue outbreak in 2016, the release was put out as a public risk communication, designed to disseminate this alert to stakeholders and the community, and advise the public on what they could do to suppress the mosquito population, such as taking appropriate precautions to prevent mosquito breeding. Risk communication is an integral part of any public health programme and it is not done lightly. It is a fundamental part of the Singapore dengue control programme which strongly focuses on interepidemic surveillance and control, risk-based prevention and intervention, and coordinated intersectoral cooperation.[6]

Internally, NEA has stepped up its outbreak response to the heightened threat alert. This includes enhanced vector surveillance with the assistance of additional temporary officers to augment the regular vector control workforce. Since then, over 350,000 home inspections have been performed, with over 3000 *Aedes* breeding sites containing approximately 100,000 larvae, removed. Islandwide Gravitrap surveillance, where 30,000 traps across 5000 Housing and Development Board (HDB) blocks have been deployed, has also removed over 20,000 adult *Aedes* mosquitoes. The risk analysis prompted NEA's earlier outbreak preparation, including stockpiling of diagnostic kits, insect repellent and insecticides.

The recent decline in dengue cases noted by Kalimuddin et al is of course highly encouraging. Though climatological drivers could have contributed to this fall, the combined impact of participation in source reduction from the community and stakeholders must be given due credit. After all, the low dengue seroprevalence of the local population and low endemicity testifies to the positive impact of such integrated vector management practice in Singapore.[8] The low seroprevalence rate among Singapore residents[9] puts Singapore in the unusual situation of being a low transmission area with a low force of infection,[10] despite being a location that is highly suited to high *Aedes* endemicity. Nevertheless, Singapore cannot rest on its laurels. The typical dengue season is approaching and a high number of cases prior to the season could serve as a launching pad that quickly drives dengue cases to epidemic levels.

As the statistician, Dr George EP Box, wisely said: "Essentially, all models are wrong, but some are useful". The use of prediction models for risk analysis and decision-making in public health is a catch-22 situation. If the outbreak occurs as predicted, it may be perceived that intervention measures were insufficient or ineffective, as they failed to mitigate the heralded outbreak, but if the actual case count is lower or higher than predicted, it is natural to infer that the model itself was inaccurate. It is clearly not feasible to observe what would happen in the absence of control efforts and validate predictions of large epidemics that require a strong response; this is one reason why no forecaster would ever claim absolute certainty, especially when pertaining to complex biological, ecological, meteorological and environmental systems, such as those governing dengue transmission. Modelling output, as much as other signs of an impending outbreak such as mosquito numbers or meteorological data, has a role to play in guiding—but not dictating—policy, and public health authorities and policy makers should not be deterred from using prediction models to guide risk communications, outbreak preparation and response.

REFERENCES

1. National Environment Agency. Dengue cases may exceed 30,000 in 2016. Available at: http://www.nea.gov.sg/corporate-functions/newsroom/news-releases/category/public-health/dengue-cases-may-exceed-30000-in-2016. Accessed on 10 May 2016.
2. Shi Y, Liu X, Kok SY, Rajarethinam J, Liang S, Yap G, et al. Three-month real-time dengue forecast models: an early warning system for outbreak alerts and policy decision support in Singapore. Environ Health Perspect 2015. [Epub ahead of print].
3. Yap GSHL, Hapuarachchi C, Chong CS, Tan LK, Liu X, Shi Y, et al. Dengue outlook for Singapore in 2016. Available at: https://www.moh.gov.sg/content/dam/moh_web/Statistics/Epidemiological_News_Bulletin/2016/ENB%20Quarterly_Jan%202016.pdf. Accessed on 10 May 2016.
4. van Panhuis WG, Choisy M, Xiong X, Chok NS, Akarasewi P, Iamsirithaworn S, et al. Region-wide synchrony and traveling waves of dengue across eight countries in Southeast Asia. Proc Natl Acad Sci U S A 2015;112:13069-74.

5. Lee KS, Lai YL, Lo S, Barkham T, Aw P, Ooi PL, et al. Dengue virus surveillance for early warning, Singapore. Emerg Infect Dis 2010;16:847-9.
6. Ng LC, Tan HK, Tan LK, Chong CS, Ho D. Evolving dengue control programme in Singapore. Available at: https://www.moh.gov.sg/content/dam/moh_web/Statistics/Epidemiological_News_Bulletin/2016/ENB%20Quarterly_Jan%202016.pdf. Accessed on 10 May 2016.
7. The Straits Times. Dengue is a community battle. 9 April 2013. Available at: http://www.who.int/immunization/sage/meetings/2016/april/1_Background_Paper_Dengue_Vaccines_2016_03_17.pdf. Accessed on 10 May 2016.
8. World Health Organization. Background paper on dengue vaccines. Available at: http://www.who.int/immunization/sage/meetings/2016/april/1_Background_Paper_Dengue_Vaccines_2016_03_17.pdf. Accessed on 10 May 2016.
9. Low SL, Lam S, Wong WY, Teo D, Ng LC, Tan LK. Dengue seroprevalence of healthy adults in Singapore: serosurvey among blood donors, 2009. Am J Trop Med Hyg 2015;93:40-5.
10. Imai N, Dorigatti I, Cauchemez S, Ferguson NM. Estimating dengue transmission intensity from sero-prevalence surveys in multiple countries. PLoS Negl Trop Dis 2015;9:e0003719.

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Reply to "Use of Prediction Models for Risk Analysis and Decision-Making in Public Health—The Catch-22 Conundrum"

We are pleased that our editorial[1] has triggered a debate on the usefulness of prediction models to guide disease preventive operations. Indeed, we believe that any disease preventive programme should be regularly and critically reviewed to ensure that the approaches to protect our population are firmly grounded on all available evidence.

Mathematical models have and will continue to impact on our understanding of disease epidemiology as well as generate new hypotheses that shape studies to improve disease prevention. The question before us is whether such models are ready to be applied as predictive tools for epidemics to scale the intensity of control measures. While the authors have acknowledged that mathematical models are imperfect, they contend that such predictive models should still nonetheless be used to guide disease control operations. As an example, they reported their recent experience in having removed more than 20,000 adult mosquitoes using their Gravitrap, as well as stockpiling of diagnostic kits, insecticides and insect repellents. While this is indeed laudable, it also raises the question of what would happen if the model inaccurately predicts low dengue incidence for the year?

The use of mathematical models to predict disease incidence and guide public health operations is, in many ways, similar to the development of biomarkers as prognostic tools to guide case management. Demonstration of statistically robust, reproducible sensitivity and specificity is an absolute requirement, both from a scientific and ethical standpoint, before any biomarker can be applied clinically. Can similar studies be carried out to demonstrate the robustness of any predictive models?

Indeed, this was a question that was addressed recently, shortly after our editorial was published in April this year. Reich and colleagues developed a real-time forecasting model for dengue and applied it in 77 provinces in Thailand.[2] The authors observed mixed performance of the model across the provinces. Their finding suggests heterogeneity in the various factors that influence the performance of their model, making prospective validation of any predictive model through studies in different countries or regions, difficult. These findings also suggest that models that are tailored to cater to the nuances in each geographic location, such as the one described by the National Environment Agency (NEA), could have greater accuracy in prediction compared to models that apply generic parameters. However, statistical validation of such models will require long periods of prospective testing for robustness.

Perhaps it may be more helpful to compare predictive models that cater to the uniqueness of a specific locality, such as Singapore, to personalised medicine. Personalised medicine stratifies disease into different groups for management, based on a plethora of genetic, protein or even metabolomic signatures. In such instances, biomarkers are identified from the molecules that play key mechanistic roles in pathogenesis, which is especially useful when the prevalence of cases that display specific bio-signatures, is low. Here, the similarity between predictive models and personalised medicine ends; unlike biomarkers that are grounded on disease mechanisms, predictive models rely on parameters that have shown statistical association with, but not causation of dengue epidemics.

The factors that influence dengue transmission and hence, risk of epidemics, are not completely understood. Herd immunity against each of the 4 dengue virus (DENV) serotype, as pointed out by the authors, obviously plays a major role. Indeed, we and others have examined how the low herd immunity, as a consequence of the low *Aedes* mosquito population density in Singapore have profoundly shaped the re-emergence of dengue in Singapore.[3-6] A less well-defined but probably underestimated factor is the fitness of the virus. DENVs are not monolithic; genomic differences give rise to strains that differ in epidemiological fitness. We showed recently that as few as 3 nucleotide substitutions in the 3' untranslated region (3'UTR) of the DENV genome altered the ability of the virus to suppress interferon induction.[7] The reduced interferon expression during infection contributed, at least in part, to the ability of this strain of DENV to spread epidemically in Puerto Rico in 1994.[7] Likewise, alterations in the 3'UTR sequence also could have contributed to another outbreak in Nicaragua in 2005.[7,8] However, the science that links genetic mechanisms to epidemic transmission is still in its infancy and thus, not sufficiently mature to be incorporated into predictive models. Consequently, the fitness of circulating strains of DENV could be a major

confounding factor of the accuracy of current predictive models. It is thus plausible that emergence or introduction of an epidemiologically fit DENV could cause a major epidemic despite prediction of low dengue incidence based on climatic and other parameters considered in the model.

Mathematical models have exciting potential to be used as tools to predict disease incidence and guide or scale disease control measures accordingly. However, for mathematical models to be used in such a manner to safeguard our population's health, the quality of evidence for the use of such tools should meet the same rigour as prognostic biomarkers for case management. Until then, we believe that reduction of *Aedes* larval habitats regardless of the risk of epidemics, which is a strategy that has served Singapore well for decades,[4] should continue to remain the emphasis of our dengue prevention programme. In that, there is no conundrum.

REFERENCES

1. Kalimuddin S, Low JG, Ooi EE. Dengue disease modelling and forecasting: utility and limitations. Ann Acad Med Singapore 2016;45:121-2.
2. Reich NG, Lauer SA, Sakrejda K, Iamsirithaworn S, Hinjoy S, Suangtho P, et al. Challenges in real-time prediction of infectious disease: a case study of dengue in Thailand. PLoS Negl Trop Dis 2016;10:e0004761.
3. Ooi EE, Hart TJ, Tan HC, Chan SH. Dengue seroepidemiology in Singapore. Lancet 2001;357:685-6.
4. Ooi EE, Goh KT, Gubler DJ. Dengue prevention and 35 years of vector control in Singapore. Emerg Infect Dis 2006;12:887-93.
5. Egger JR, Ooi EE, Kelly DW, Woolhouse ME, Davies CR, Coleman PG. Reconstructing historical changes in the force of infection of dengue fever in Singapore: implications for surveillance and control. Bull World Health Organ 2008;86:187-96.
6. Low JG, Ooi EE. Dengue—old disease, new challenges in an ageing population. Ann Acad Med Singapore 2013;42:373-5.
7. Manokaran G, Finol E, Wang C, Gunaratne J, Bahl J, Ong EZ, et al. Dengue subgenomic RNA binds TRIM25 to inhibit interferon expression for epidemiological fitness. Science 2015;350:217-21.
8. OhAinle M, Balmaseda A, Macalalad AR, Tellez Y, Zody MC, Saborio S, et al. Dynamics of dengue disease severity determined by the interplay between viral genetics and serotype-specific immunity. Sci Transl Med 2011;3:114ra28.

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Comparison of the Haemodynamic Parameters of Venous and Arterial Coronary Artery Bypass Conduits

Dear Editor,

Coronary artery bypass grafting (CABG) is an established revascularisation treatment for patients with coronary artery disease (CAD). However, the graft patency rate varies significantly among different bypass graft conduits. Ten years after CABG, more than 90% of the left internal mammary artery (LIMA) grafts are patent[1] but the patency rate of saphenous vein grafts (SVGs) ranges from 40% to 50%.[2] Radial artery (RA) grafts have better long-term patency than SVGs.[3]

The pathogenetic mechanisms responsible for the early development of thrombosis, intimal hyperplasia (IH) and atherosclerosis in grafts remain elusive. Physicians generally believe that haemodynamic forces on blood vessels, especially wall shear stress (WSS), play an important role in initiating the process of atherosclerosis.[4,5] Signalling pathways have been proposed to mediate the mechanochemical transduction in endothelial cells in response to disturbed flow and WSS.[6]

Recent developments in transit time flowmetry (TTFM) not only provide intraoperative mean graft flow (MGF), pulsatility index (PI) and diastolic filling (DF) measurements, but also provide a foundation for estimating WSS from the MGF and graft diameter. We hypothesise that WSS may play a role in graft patency and the purpose of this study was to examine the relationship between graft conduit types and haemodynamic parameters, such as MGF, PI, DF and WSS.

Materials and Methods

The study was approved by the local ethics committee. We recruited 38 patients who had undergone CABG with TTFM of bypass grafts. All surgeries were performed following a standard protocol. Graft and coronary vessel diameters were measured using a surgical metal probe.

TTFM measurements were performed for all the patients with either MEDISTIM VeriQTM or VeriQTM C system, which provided MGF (time-averaged graft flow rate, mL/min), PI (the pulsatility of flow, calculated as PI = maximum flow - minimum flow/mean flow) and DF (the fraction of diastolic volume flow to total flow) as shown in Figure 1.

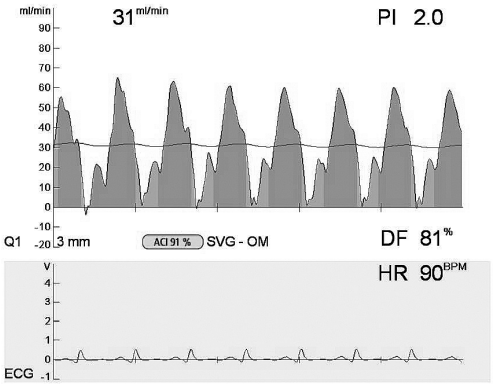

Fig. 1. A representative transit time flowmetry (TTFM) record for a coronary artery bypass grafting (CABG) patient. A typical curve has an M-shape. The blue and the red colours represent the flow during diastolic and systolic phases, respectively.

Using a modified Hagen-Paiseuille equation,[7] WSS was calculated as:

$$WSS = \frac{32\mu Q}{\pi D^3}$$

where μ was the blood viscosity, 0.0035 kg/m•s. Q and D represented the MGF and graft diameter respectively.

All data were grouped according to the bypass type: LIMA, SVG and RA. One-way analysis of variance (ANOVA) was used to compare the continuous data of these 3 groups. Non-linear regression was used to quantity the association between 2 continuous variables. All statistical analyses were performed using SPSS Version 21 software.

Results

A total of 38 patients were studied, with mean age at 60 ± 8 years and median heart rate of 75 ± 13/min. Thirty-one patients (81.6%) had hyperlipidaemia, 29 (76.3%) had hypertension, 13 had diabetes mellitus (34.2%) and 5 (13.2%) had prior myocardial infarction. TTFM measurements were performed on 89 grafts: 35 LIMA, 45 SVG and 9 RA. No significant differences in patient characteristics (age, sex, BMI, coronary risk factors, presurgery left ventricular ejection fraction (LVEF) or medical history) were observed among the 3 groups of patients (with LIMA, SV and RA grafts) separately.

Table 1. Haemodynamic Data

	LIMA	SV	RA	*P* Value
MGF (mL/min)	25 ± 13	39 ± 21	28 ± 18	0.004
PI	2.7 ± 1.1	3.0 ± 1.8	2.0 ± 0.6	0.178
DF (%)	76 ± 8	66 ± 11	70 ± 7	<0.001
Graft diameter (mm)	1.8 ± 0.4	3.7 ± 0.6	2.6 ± 0.5	<0.001
WSS (dyn/cm^2)	30.2 ± 22.9	4.6 ± 2.1	10.1 ± 6.4	<0.001

DF: Diastolic filling; MGF: Mean graft flow; LIMA: Left internal mammary artery; PI: Pulsatility index; RA: Radial artery; SV: Saphenous vein; WSS: Wall shear stress

In general, median MGF, PI and DF values for all graft types (LIMA: MGF = 25 mL/min, PI = 2.7, DF = 76%; SV: MGF = 39 mL/min, PI = 3.0, DF = 66%; RA: MGF = 28 mL/min, PI = 2.0, DF = 70%) were all satisfactory (Table 1) according to TTFM guidelines[8] of MGF >15 mL/min, PI <5 and DF >25%. Graft types were observed to significantly affect MGF (Q) (P = 0.004) and DF (P <0.001), but no PI (P >0.05).

SVG had slightly higher MGF (39 ± 21 mL/min) than that of LIMA (25 ± 13 mL/min) or RA (28 ± 18 mL/min) grafts. Lower DF was found for SV (66 ± 11%) than that of LIMA (76 ± 8%) or RA (70 ± 7%) grafts. These observations were congruent with data reported by Kieser et al[8] who studied TTFM in 336 consecutive patients (Fig. 2). Because they only reported the data of grafts with PI ≤5 and had only a small sample size of SVG (n = 15), there was smaller variation ranges of their data in contrast to ours.

Graft diameters significantly differed among the 3 graft types (P <0.001) (Table 1). SVG had larger diameter (3.7 ± 0.6 mm) than either LIMA (1.8 ± 0.4 mm) or RA (2.6 ± 0.5 mm). The observed diameters of grafts were close to the values reported by Shimizu et al.[7] Significant differences were found in WSS for the 3 graft types (P <0.001) (Table 1). Lower WSS was found in SVG (4.6 ± 2.1 dyn/cm^2) than either LIMA (30.2 ± 22.9 dyn/cm^2) or RA (10.1 ± 6.4 dyn/cm^2), which was in agreement with an intravascular Doppler-tipped angioplasty study.[9] Similar WSS values of SVG (5 ± 2 dyn/cm^2) was reported by a postoperative coronary angiography study.[7] There was significant non-linear relationship found between WSS and graft diameter for LIMA and SVG (P <0.05). This inverse relationship between WSS and graft diameter could be explained by the Hagen-Paiseuille[7] equation, which states that WSS is inversely proportional to the third power of the internal radius.

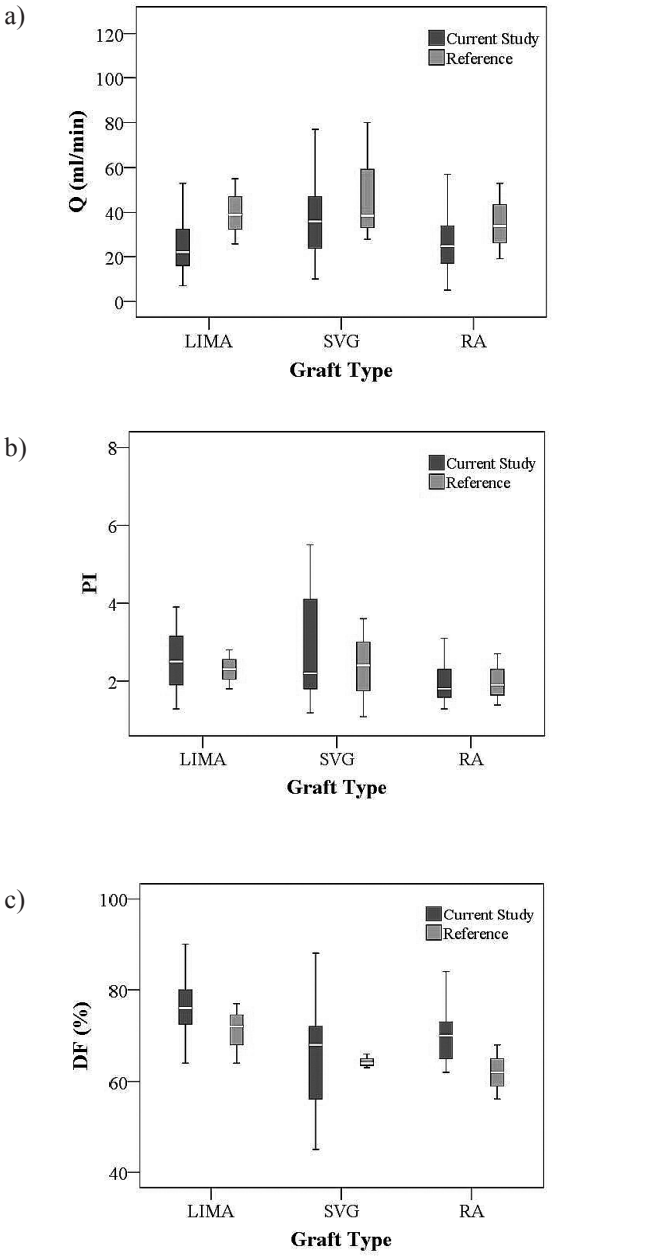

Fig. 2. Comparisons of a) MGF, mean graft flow; b) PI, pulsatility index; and c) DF, diastolic filling between current and reported[8] studies.

Discussion

It has been speculated that WSS may be one of the major factors affecting graft patency. Local low WSS (<4 dyn/cm^2) was observed to lead to increase of platelet activation, vasoconstriction, oxidative state and cellular turnover, which may result in the switching of arterial endothelial phenotypes from atheroprotective to atherogenic.[10] In vitro experiments that subjected human saphenous vein to laminar flow reported that neointima formation was completely inhibited[11] when WSS = 9 dyn/cm^2 and only partly suppressed when WSS = 1 dyn/cm^2. In this study, WSS of SVGs was found to be significantly smaller than either LIMA or RA, and it varied between 2.5 and 6.7 (dyn/cm^2); 42% of SVGs had

WSS <4 dyn/cm^2. Therefore lower WSS of the SVG may be associated with initiation of intimal hyperplasia and/or atherosclerotic signalling and processes that induce graft failure and lead to lower graft patency rate of SVG[12] than LIMA and RA grafts.

As graft diameter was found to have an inverse relationship with WSS, smaller diameter of SVG was believed to lead to higher (and desirable) WSS and may finally result in the improvement of graft patency rate. This observation is consistent with some studies, which demonstrated that large vein calibre was associated with poor patency.[13]

Discordance was observed when researchers attempted to link their TTFM measured data (MGF, PI and DF) with graft patency rates.[8,13] The results of our study lend support to the usefulness of assessing WSS from intraoperative TTFM for better prediction of graft patency. The recent emergence of new TTFM technology not only allows the measurement of intraoperative flow parameters, but also enables the capture of intraoperative epicardial images, which can help in determining graft diameter and calculate WSS of grafts in real time during the surgery.

Strengths of this study include the linking WSS of grafts with the different types of graft conduits. The main limitation of this study is that WSS was estimated from Hagen-Paiseuille equation and it might not be as accurate as values derived from numerical simulations on 3D patient-specific models reconstructed from computed tomography (CT) and/or magnetic resonance imaging (MRI) images.[14] Nevertheless this method has been used in previous studies.[7,15] We believe that the WSS calculated in this study provides a good benchmark for comparison among the 3 types of bypass conduits.

Conclusion

In this study, lower WSS was found for SVGs than for either LIMA or RA grafts. WSS of SVG varied between 2.5 and 6.7 (dyn/cm^2) and 42% of SVGs had WSS <4 dyn/cm^2. Low WSS associated with SVG was conjectured to result in the generation of atherosclerosis and graft stenosis. Appropriate selection of SV segment with suitable calibre is thus necessary to accommodate physiological WSS, which may help improve SVG patency rate.

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REFERENCES

1. Fitzgibbon GM, Kafka HP, Leach AJ, Keon WJ, Hooper GD, Burton JR. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. J Am Coll Cardiol 1996;28:616-26.
2. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, et al. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;124:e652-e735.
3. Cohen G, Tamariz MG, Sever JY, Liaghati N, Guru V, et al. The radial artery versus the saphenous vein graft in contemporary CABG: a case-matched study. Ann Thorac Surg 2001;71:180-6.
4. Owida AA, Do H, Morsi YS. Numerical analysis of coronary artery bypass grafts: an overview. Comput Methods Programs Biomed 2012;108:689-705.
5. Freshwater IJ, Morsi YS, Lai T. The effect of angle on wall shear stresses in a LIMA to LAD anastomosis: numerical modelling of pulsatile flow. Proc Inst Mech Eng H 2006;220:743-57.
6. Chiu JJ, Chien S. Effects of disturbed flow on vascular endothelium: pathophysiological basis and clinical perspectives. Physiol Rev 2011;91:327-87.
7. Shimizu T, Ito S, Kikuchi Y, Misaka M, Hirayama T, Ishimaru S, et al. Arterial conduit shear stress following bypass grafting for intermediate coronary artery stenosis: a comparative study with saphenous vein grafts. Eur J Cardiothorac Surg 2004;25:578-84.
8. Kieser TM, Rose S, Kowalewski R, Belenkie I. Transit-time flow predicts outcomes in coronary artery bypass graft patients: a series of 1000 consecutive arterial grafts. Eur J Cardio-thoracic Surg 2010;38:155-62.
9. Bach RG, Kern MJ, Donohue TJ, Aguirre FV, Caracciolo EA. Comparison of phasic blood flow velocity characteristics of arterial and venous coronary artery bypass conduits. Circulation 1993;88:II133-40.

10. Asakura T, Karino T. Flow patterns and spatial distribution of atherosclerotic lesions in human coronary arteries. Circ Res 1990;66:1045-66.
11. Porter KE, Nydahl S, Dunlop P, Varty K, Thrush AJ, London NJ. The development of an in vitro flow model of human saphenous vein graft intimal hyperplasia. Cardiovasc Res 1996;31:607-14.
12. Do H, Amal AO, Yang W, Morsi YS. Numerical simulation of the haemodynamics in end-to-side anastomoses. Int J Numer Methods Fluids 2011;67:638-50.
13. Lehnert P, Møller CH, Damgaard S, Gerds TA, Steinbrüchel DA. Transit-time flow measurement as a predictor of coronary bypass graft failure at one year angiographic follow-up. J Card Surg 2015;30:47-52.
14. Zhang JM, Zhong L, Su B, Wan M, Yap JS, Tham JP, et al. Perspective on CFD studies of coronary artery disease lesions and hemodynamics: a review. Int J Numer Methods Biomed Eng 2014;30:659-80.
15. Papaioannou TG, Stefanadis C. Vascular wall shear stress: basic principles and methods. Hellenic J Cardiol 2005;46:9-15.

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Circulating Microparticle Double-Stranded Deoxyribonucleic Acid in Systemic Lupus Erythematosus

Dear Editor,

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with complex pathogenesis which is yet to be completely understood. Since the original discovery of anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies, the general result from intense research has been that native mammalian dsDNA is not immunogenic, even if presented with complete Freund's adjuvant.[1-3] This is despite an antigen-driven response as evidenced by the clonality of anti-dsDNA antibodies and patterns of random somatic mutations in both patients and murine models of SLE to suggest that DNA is the selecting antigen.[2,4] These studies demonstrate that mechanisms for the production of anti-dsDNA antibodies and their affinity maturation toward anti-dsDNA specificity are operational in SLE patients.[4] The question that arises is what transforms DNA to the immunogenic form in patients with SLE. Microparticles (MPs) represent a heterogeneous population of membrane-bound vesicles with a diameter of 0.1 μm to 1 μm that are released by the budding of plasma membrane and express antigens specific of their parental origin.[5] The release of MPs by various cell types is a ubiquitous process that gets accelerated during cellular activation and apoptosis.[5] Upon initiation, translocation of phosphatidylserine from the inner to outer surface leaflet of the plasma membrane results in loss of normal phospholipid asymmetry.[5] As shown in cell lines undergoing in vitro apoptosis, DNA is sequestered into granules and then packaged into separate apoptotic bodies.[6] Whereas the mechanism mediating this cellular rearrangement is not known, the end result is the repositioning of nuclear constituents in a form that may be more accessible to the immune system.[7] We hypothesise that in this model, MPs may provide a framework to intensify the immunogenicity of the component DNA to induce anti-dsDNA antibody production and therefore, the aim of the present study was to evaluate the putative role of DNA within MPs (MP DNA) as the circulating antigenic target.

The study was cross-sectional in design. Fourteen unselected patients (12 women and 2 men) fulfilling at least 4 of the American College of Rheumatology 1997 revised classification criteria for SLE were included.[8] Disease activity was assessed using the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-modified SLE Disease Activity Index (SLEDAI).[9] Eight healthy female individuals were included as control subjects. Anti-dsDNA immunoglobulin G (IgG) titers, measured using indirect enzyme-linked immunosorbent assay (Bio-Rad, Hercules, CA, US), and other disease markers were performed by the clinical laboratory of National University Hospital. Circulating MPs were obtained from platelet-free plasma (PFP) obtained by successive centrifugations of venous blood. PicoGreen (Invitrogen, Waltham, MA, US), a membrane-permeable dsDNA specific dye, was used to label the MP samples. We analysed the samples on FACSCalibur flow cytometer (BD Biosciences, Franklin Lakes, NJ, US). An initial MP-size gate was set with the help of calibrating fluorescent 0.22 μm, 0.45 μm, 0.88 μm and 1.34 μm polystyrene beads (Spherotech, Lake Forest, IL, US). MP DNA were enumerated on the SSC/FL1 plot and defined as events that were sensitive to differential detergent lysis using 0.05% Triton X-100. Therefore, each detergent-sensitive FL1-positive event on the SSC/FL1 plot was considered as 1 MP DNA. Plasma concentrations (MP DNA/μL) were calculated according to the actual flow rate of the flow cytometer, MP DNA count per unit of time and net dilution during sample preparation of the analysed sample. No distinct population of detergent-sensitive MPs on the SSC/FSC plot could be gated to measure total MP numbers. Some samples were treated with 1 U of RNase-free DNase (Promega, Fitchburg, WI, US) for 20 min at 37°C to assess sensitivity of MP DNA to DNase I.

We identified MP DNA in PFP, based on fluorescence and detergent sensitivity (Figs. 1a and 1b). With this approach, extracellular DNA (plasma DNA) not associated with MPs were also detected in PFP. Importantly, although plasma DNA remained intact after detergent treatment, MPs containing DNA were detergent-soluble, establishing their phospholipid composition. To evaluate if MP DNA is resistant to DNase activity, MPs were treated with DNase I, counterstained with PicoGreen and then analysed using flow cytometry. There was a reduction of MP DNA count following DNase I treatment (Fig. 1c). Further treatment with 0.05% Triton X-100 led to complete solubilisation of MP DNA by detergent (Fig. 1d). Thus, DNA packaged within MPs is protected from DNase activity. The median concentration of MP DNA/μL in PFP of the 14 SLE patients was significantly higher than the 8 healthy controls (2460.28 [Q1; Q3 1010.91; 3416.26] vs 403.73 [Q1; Q3 222.26; 1801.88]; $P = 0.020$) (Fig. 2). The median age of the SLE patients was 39.5 (Q1; Q3 25.0; 54.8), with a median disease

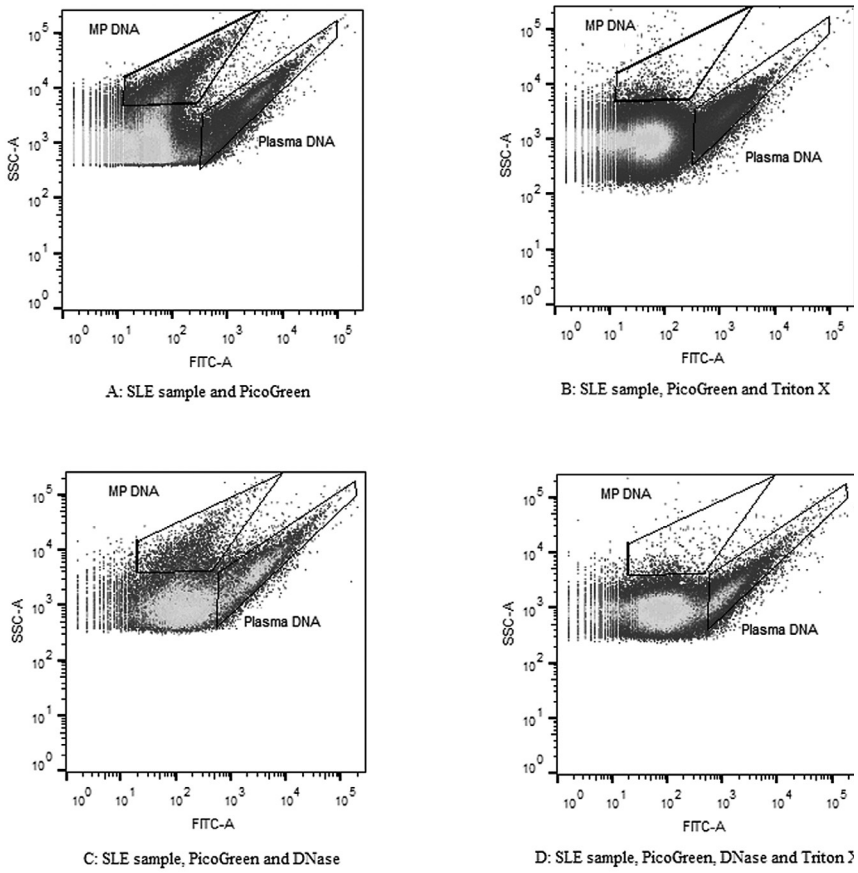

Fig. 1. Demonstration of MP DNA through representative flow cytometry analysis in plasma from an SLE patient. Using PicoGreen labelling, 2 distinct populations of FITC+ nanoparticles were obtained. The more granular population was sensitive to 0.05% Triton X-100 detergent, indicating that this population of FITC+ nanoparticles were MPs with membrane phospholipids (MP DNA count = 9203 in Fig. 1a and MP DNA count = 806 in Fig. 1b). Using DNase I, the MP DNA population decreased (MP DNA count = 1686 in Fig. 1c), demonstrating that DNA packaged within MPs is protected from DNase activity. With the addition of 0.05% Triton X-100, the MP DNA population which was resistant to DNase I is now solubilised (MP DNA count = 420 in Fig. 1d).

duration of 24.5 years (Q1; Q3 17.0; 42.5) and a median SELENA-SLEDAI score of 7.0 (Q1; Q3 5.3; 15.3). The median age of healthy controls was 33.5 years (Q1; Q3 25.0; 43.5). The concentration of MP DNA positively correlated with anti-dsDNA IgG (r [10] = 0.806, $P = 0.005$) (Fig. 3) after exclusion of outliers, which may be consistent with MP DNA as an antigenic source for anti-dsDNA IgG formation. However, MP DNA did not correlate with complement levels or SELENA-SLEDAI scores.

The results from this study provide new perspectives on the presence of extracellular DNA in SLE patients and healthy controls. Using flow cytometry, MP DNA were visualised and enumerated in the PFP of SLE patients and healthy controls. In the form of MPs, DNA likely exists on both the surface and interior.[10] This would account for the observation of DNA packaged within MPs being protected from DNase activity.[11] Further, plasma DNA not associated with MPs were detected in both SLE patients and healthy controls. Experiments to assess the origins of plasma DNA and its sensitivity to DNase I were not performed in the current study. The most striking finding in this study is the marked difference in the concentration of MP DNA in SLE patients compared to healthy controls. Although the increased MP numbers suggest a role in SLE immunopathogenesis, elucidating this role is difficult at present. Ullal et al showed some increase in the total number of MP and increase in IgG positive MPs in SLE patients compared to healthy controls.[12] Nielsen et al showed that MP populations that do not bind annexin V are increased whereas total number of MP and annexin V-binding MPs are decreased in SLE patients compared to healthy controls.[13] We showed a correlation between MP DNA concentration and anti-dsDNA IgG titers. Ullal et al and Nielsen et al showed a correlation between the number of IgG-positive MPs and anti-DNA levels in SLE patients.[12,14] However, their findings did not demonstrate that the bound IgG antibody was anti-dsDNA IgG. In this regard, IgG positive MPs can also occur in the synovial fluid of rheumatoid arthritis patients.[12,15] Hence, to our knowledge, this is the first study to demonstrate the presence of MP DNA definitively in the

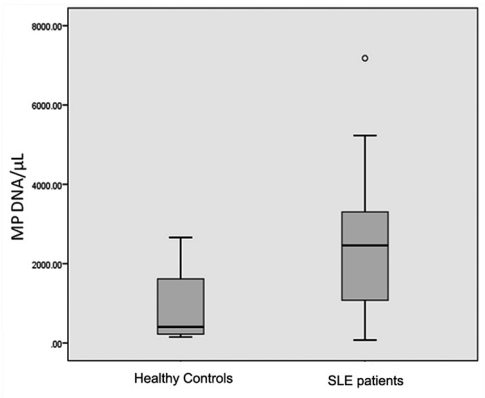

Fig. 2. Concentration of MP DNA in SLE patients and healthy controls. The median MP DNA/µL of plasma for 14 SLE patients was significantly higher than the 8 healthy controls.

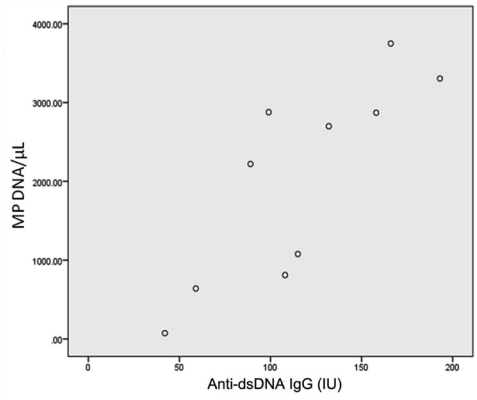

Fig. 3. The relationship between MP DNA and anti-dsDNA levels in the plasma of SLE patients. There was significant correlation of MP DNA concentration with anti-dsDNA IgG titers.

plasma of SLE patients. The correlation with anti-dsDNA IgG suggests that MP DNA may be a source of immunogenic autoantigen for the production of anti-dsDNA antibodies and our results support this idea. Further studies will refine the role of MP DNA in the pathogenesis, perpetuation and modulation of disease activity in SLE.

REFERENCES

1. Celada F. The anti-DNA story. Lupus 2011;20:553-5.
2. Pisetsky DS. The origin and properties of extracellular DNA: from PAMP to DAMP. Clin Immunol 2012;144:32-40.
3. Rekvig OP, Mortensen ES. Immunity and autoimmunity to dsDNA and chromatin–the role of immunogenic DNA-binding proteins and nuclease deficiencies. Autoimmunity 2012;45:588-92.
4. Rekvig OP, Nossent JC. Anti-double-stranded DNA antibodies, nucleosomes, and systemic lupus erythematosus: a time for new paradigms? Arthritis Rheum 2003;48:300-12.
5. Mause SF, Weber C. Microparticles: protagonists of a novel communication network for intercellular information exchange. Circ Res 2010;107:1047-57.
6. Halicka HD, Bedner E, Darzynkiewicz Z. Segregation of RNA and separate packaging of DNA and RNA in apoptotic bodies during apoptosis. Exp Cell Res 2000;260:248-56.
7. Pisetsky DS, Ullal AJ, Gauley J, Ning TC. Microparticles as mediators and biomarkers of rheumatic disease. Rheumatology (Oxford) 2012;51:1737-46.
8. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
9. Petri M, Kim MY, Kalunian KC, Grossman J, Hahn BH, Sammaritano LR, et al. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med 2005;353:2550-8.
10. Pisetsky DS, Lipsky PE. Microparticles as autoadjuvants in the pathogenesis of SLE. Nat Rev Rheumatol 2010;6:368-72.
11. Orozco AF, Jorgez CJ, Horne C, Marquez-Do DA, Chapman MR, Rodgers JR, et al. Membrane protected apoptotic trophoblast microparticles contain nucleic acids: relevance to preeclampsia. Am J Pathol 2008;173:1595-608.
12. Ullal AJ, Reich CF 3rd, Clowse M, Criscione-Schreiber LG, Tochacek M, Monestier M, et al. Microparticles as antigenic targets of antibodies to DNA and nucleosomes in systemic lupus erythematosus. J Autoimmun 2011;36:173-80.
13. Nielsen CT, Ostergaard O, Johnsen C, Jacobsen S, Heegaard NH. Distinct features of circulating microparticles and their relationship to clinical manifestations in systemic lupus erythematosus. Arthritis Rheum 2011;63:3067-77.
14. Nielsen CT, Ostergaard O, Stener L, Iversen LV, Truedsson L, Gullstrand B, et al. Increased IgG on cell-derived plasma microparticles in systemic lupus erythematosus is associated with autoantibodies and complement activation. Arthritis Rheum 2012;64:1227-36.
15. Cloutier N, Tan S, Boudreau LH, Cramb C, Subbaiah R, Lahey L, et al. The exposure of autoantigens by microparticles underlies the formation of potent inflammatory components: the microparticle-associated immune complexes. EMBO Mol Med 2013;5:235-49.

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Lumbar Radiculopathy – Incremental Value of Magnetic Resonance Neurography over Non-Contributory Magnetic Resonance Imaging

Dear Editor,

Lumbar radiculopathy is defined in terms of symptoms (including pain and paraesthesia) and signs (including weakness) in the distribution of a spinal nerve root. Compression of the nerve root, possibly leading to inflammation, is a common aetiology. Magnetic resonance imaging (MRI) is the preferred imaging modality used for evaluation of patients with lumbar radiculopathy. It serves as a useful adjunct to electrodiagnostic testing, which include electromyography (EMG) and nerve conduction studies. MRI has been shown to provide excellent inter-observer agreement for the diagnosis of nerve root compression in patients with radiculopathy.[1] However, a management dilemma frequently occurs when a patient with clinical features of radiculopathy has normal or non-contributory MRI findings. In this article, we report a patient with Parkinson's disease who presented with features of lumbar radiculopathy and subsequently underwent MRI lumbar spine examination, which was inconclusive. The final diagnosis was made using high resolution magnetic resonance neurography (MRN) of the lumbosacral plexus, which employed 2-dimensional (2D) and isotropic 3D imaging sequences.

Case Report

A 78-year-old male, previously diagnosed with Parkinson's disease, presented to the clinic with progressive gait disturbance. He had a history of twisting his back 1 week prior and thereafter, developed left leg weakness and radicular pain radiating from his back to his groin and left hip. On examination, there was weakness on left hip flexion, left knee extension and absence of left knee jerk. Left lumbar radiculopathy was clinically suspected to be the cause of his gait dysfunction, but progression of his Parkinson's disease could not be ruled out as being responsible for the above findings. MRI of the lumbar spine performed outside reported multilevel disc herniations and was inconclusive of nerve compression.

MRN was performed on 3.0T MR scanner (Achieva, Philips, Best, Netherlands) using 2D axial T1W, axial T2W Dixon, 3D SHINKEI (nerve-sheath signal increased with INKed rest-tissue RARE Imaging) and diffusion tensor imaging (DTI) techniques. The study showed an extruded paracentral disk fragment arising from L3-L4 disc space on the left, extending inferiorly into the spinal canal behind the L4 vertebral body (Fig. 1), and small disc herniations at other levels. The mass effect was clearly depicted on

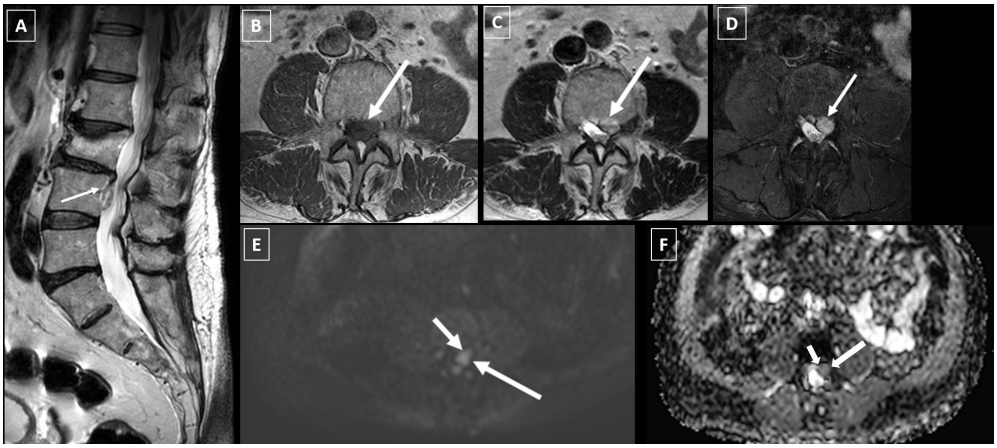

Fig. 1. Sagittal LS spine (A), axial de field of view T1W (B), T2 Dixon fat and water images (C, D) demonstrate the extruded disc at L3-4 level (arrows) compressing the thecal sac and the left preganglionic nerve root at this level. Notice smaller disc herniations at other levels. Axial DTI (b value 600, E) and ADC images (F) confirm the effacement of the left preganglionic traversing nerve root (small arrow) at this level by the disc fragment (large arrow).
ADC: Apparent diffusion coefficient; DTI: Diffusion tensor imaging

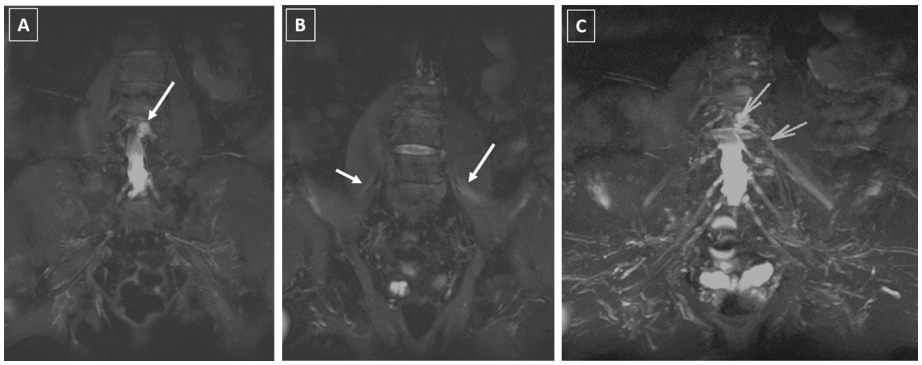

Fig. 2. Coronal 3D SHINKEI images (A, B) and MIP image (C) demonstrate the extruded disc at L3-4 level as crotch filling between the thecal sac and the preganglioninc nerve segment (arrow in A) compressing the thecal sac and the left preganglionic nerve root at this level. Notice the swollen left femoral nerve in the iliopsoas groove due to intraneural and perineural oedema (large arrow) as compared to the normal right nerve (small arrow) in B. Maximum intensity projection image (C) shows the disc (upper arrow) and the abnormal left femoral nerve (lower arrow) in 1 slab.

3D coronal SHINKEI sequence, which also showed the inflamed left femoral nerve demonstrating intraneural and perineural oedema (Fig. 2). Maximum intensity projection (MIP) oblique-angled reconstructed images created from MRN dataset on an independent work station showed the entire extent of the left femoral neuropathy and contralateral normal femoral nerve (Fig. 3). The left femoral neuropathy was qualitatively quiet conspicuous on the DTI image with effective vascular suppression due to diffusion effect and the nerve showed higher apparent diffusion coefficient (ADC = 1.3 x 10^{-3} mm^2/s) and lower fractional anisotropy (FA = 0.2) values as compared to the contralateral nerve (ADC = 1.1 x 10^{-3} mm^2/s, FA = 0.45).

Discussion

The lumbosacral (LS) plexus pathologies can be a significant source of neuropathic pain with radiculopathy versus plexopathy or underlying systemic condition, such as Parkinson's disease, thus posing a diagnostic challenge to the clinician, as in this case, due to deep location of the nerves and variable regional innervation. Classically, the diagnosis of LS radiculopathy is evaluated using electrodiagnostic testing and MRI of the lumbar spine. The high sensitivity of MRI combined with high specificity of electrodiagnostic tests often provide very good complementary information.[2] However, not infrequently, a diagnostic dilemma occurs if the MRI findings are inconclusive, e.g. in older patients with significant disc disease at multiple levels.[3] MRN can provide incremental value over electrodiagnostic tests and MRI in such cases as illustrated by this case.

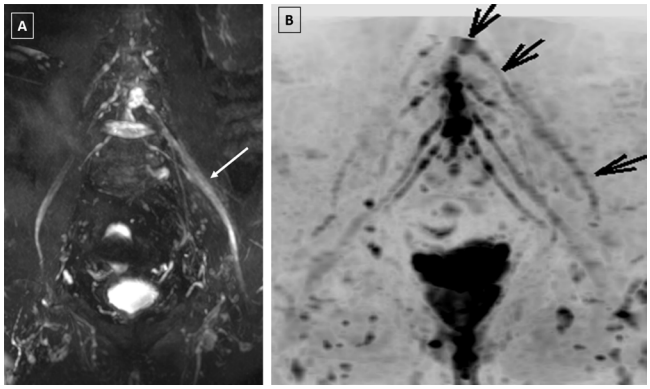

Fig. 3. Coronal anterior oblique angle reconstructed 3D SHINKEI MIP image along the femoral nerve axis at 26° (A) and DTI trace MIP image (B) demonstrates the full extent of the left femoral neuropathy (arrows).
DTI: Diffusion tensor imaging; MIP: Maximum intensity projection

MRN of the LS plexus includes sagittal and axial T2W imaging of the LS spine but replaces the conventional sagittal T1W and STIR imaging sequences by axial T1W and axial T2 fat-suppressed imaging with wider field of view encompassing the whole abdomen and pelvis with in-plane resolution of 0.5 mm and slice thickness of 4 mm. Coronal 3D inversion recovery-based variable flip angle sequence also allows a comprehensive coverage of the whole abdomen and pelvis with 1.5 mm isotropic resolution, thereby enabling high resolution multiplanar depiction of normal and abnormal peripheral nerves.[4] 3D SHINKEI imaging and DTI provide nerve selective imaging with effective vascular suppression.[5] MRN thus provides direct objective evidence of the cause (disc) and its effect (thecal sac and nerve root compression) along with depiction of the whole extent of the neuropathy corresponding to the side of symptoms (Fig. 3). MRN in addition, allows comprehensive assessment of the lumbar spine, pelvis, sacroiliac joints, hips and regional muscles, thereby not skipping over the incidental findings or neuropathy at other or contralateral levels.[6] For example, in this case, there were no other nerve abnormalities to suggest plexopathy. The regional muscles were not atrophied and there was no other mass lesion.

The MRN with DTI imaging protocol takes approximately

45 minutes on 3T scanner using front XL torso coil linked to spine coils in the back, while normal spine MR imaging takes about 30 minutes on 3T scanner. Conventional LS MR imaging should not be replaced with MRN of LS plexus on a routine basis, since it takes longer to acquire and read MRN examinations. However, the incremental value of MRN over the conventional spine MRI examinations is important to appreciate and MRN exams should be considered in the setting of non-contributory MRI in radiculopathy patients.

Conclusion

MRN of the LS plexus provides incremental value in the evaluation of patients with clinically suspected radiculopathy and non-contributory lumbar spine MRI. It can delineate the aetiology and provide direct objective evidence of neuromuscular pathology.

REFERENCES

1. Kuijper B, Beelen A, van der Kallen BF, Nollet F, Lycklama A Nijeholt GJ, de Visser M, et al. Interobserver agreement on MRI evaluation of patients with cervical radiculopathy. Clin Radiol 2011;66:25-9.
2. Barr K. Electrodiagnosis of lumbar radiculopathy. Phys Med Rehabil Clin N Am 2013;24:79-91.
3. Moore KR, Tsuruda JS, Dailey AT. The value of MR neurography for evaluating extraspinal neuropathic leg pain: a pictorial essay. AJNR Am J Neuroradiol 2001;22:786-94.
4. Delaney H, Bencardino J, Rosenberg ZS. Magnetic resonance neurography of the pelvis and lumbosacral plexus. Neuroimaging Clin N Am 2014;24:127-50.
5. Kasper JM, Wadhwa V, Scott KM, Rozen S, Xi Y, Chhabra A. SHINKEI-a novel 3D isotropic MR neurography technique: technical advantages over 3DIRTSE-based imaging. Eur Radiol 2015;25:1672-7.
6. Soldatos T, Andreisek G, Thawait GK, Guggenberger R, Williams EH, Carrino JA, et al. High-resolution 3-T MR neurography of the lumbosacral plexus. Radiographics 2013;33:967-87.

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Diffuse Indurated Skin

A healthy 60-year-old Chinese male presented with a 3-week history of progressive patchy discolouration, pain and swelling of bilateral lower limbs (left more than right), associated with constitutional symptoms of appetite loss. There was no preceding trauma, new drugs or topical applications. Clinical examination revealed extensive indurated skin over both lower limbs, extending to the inguinal fold on the left (Fig. 1). The tightness of the skin had precluded him from bending his left knee.

Magnetic resonance imaging (MRI) of the left lower limb showed diffuse skin thickening and a reticular pattern in the subcutaneous fat, in keeping with skin inflammation (Fig. 2). Blood tests were unremarkable and there was no paraproteinaemia. A malignancy workup, comprising of computed tomography (CT) of the thorax, abdomen and pelvis and endoscopic evaluations, was negative. Histology of a skin biopsy revealed mucin deposits in the dermis, thickened collagen bundles and fibroblastic proliferation.

The skin induration improved with topical application of 0.1% betamethasone valerate ointment but the patient subsequently defaulted follow-up.

What is the most likely diagnosis?

A. Systemic sclerosis
B. Scleromyxoedema
C. Nephrogenic systemic fibrosis
D. Acute lipodermatosclerosis
E. Pretibial myxoedema

Discussion

It is important to differentiate between the various conditions (such as those in options A to E) presenting clinically with indurated and hardened skin, in order to correctly identify associated underlying diseases that may be life threatening. Scleromyxoedema is the generalised form of lichen myxoedematosus, an idiopathic cutaneous disorder characterised by the proliferation of fibroblasts with excess mucin deposits in the skin, sparing the mucous membranes. The generalised form may involve internal organs and can be fatal. It is often associated with monoclonal gammopathy, or other bone marrow malignancies,[1] although not in this case.

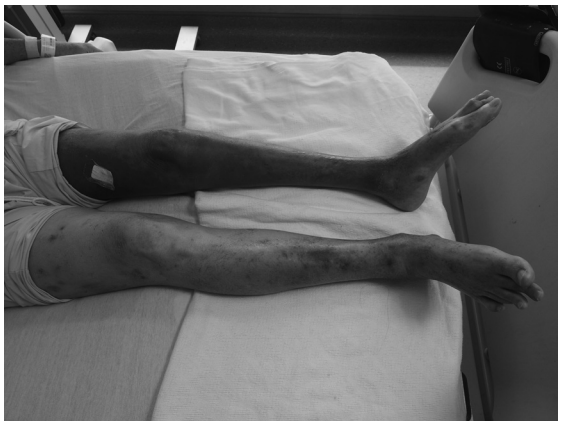

Fig. 1. Extensive indurated skin extending to the inguinal fold on the left lower limb.

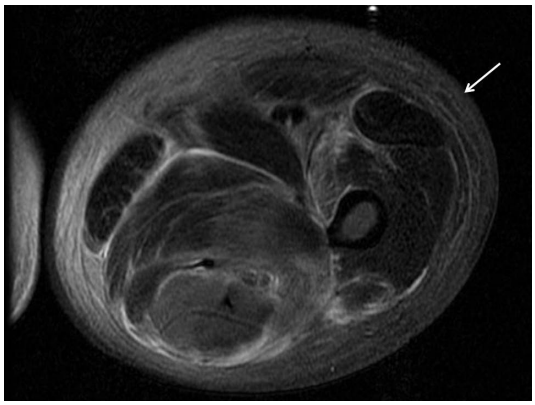

Fig. 2. Magnetic resonance imaging (MRI) images of diffuse skin thickening and a reticular pattern seen in the subcutaneous fat extending from the level of the upper thigh to the ankle.

Answer: B

The skin induration may resemble scleroderma of systemic sclerosis, but the latter is characterised by an excess production of collagen in the dermis, rather than mucin. There is no associated calcinosis or telangiectasia in scleromyxoedema.[1] Nephrogenic systemic fibrosis has almost identical histology features with scleromyxoedema, with excess mucin production and fibroblast proliferation, but occurs in patients with renal failure and may be precipitated by the use of gadolinium-containing contrast agents.[1]

Lipodermatosclerosis is a type of panniculitis that typically affects patients with venous insufficiency. In the acute inflammatory state, patients often present with swelling, skin induration and hyperpigmentation over their lower limbs, with histology revealing a lymphocytic infiltrate and tissue necrosis in the subcutaneous fat layer.[2] In pretibial myxoedema, the areas affected are localised to the anterior-lateral shins, and is almost always associated with Grave's disease.[3] The histological findings of pretibial myxoedema include increased mucin production and stellate-shaped fibroblasts, but there is no increase in the number of fibroblasts.[3]

Another much rarer condition that also causes diffuse indurated skin is scleredema, but it typically affects the upper body, and is associated with a history of a prior upper respiratory tract streptococcal infection, diabetes mellitus or monoclonal gammopathy. Histologically, scleredema is due to an excess production of both collagen and mucin in the dermis; the absence of fibroblast proliferation differentiates it from scleromyxoedema.[1]

Management of scleromyxoedema includes the evaluation of internal organ involvement and underlying malignancies. Various therapies have been tried to varying success, such as intravenous immunoglobulin, thalidomide and corticosteroids.[1]

Conclusion

Diseases resulting in hardening of the skin are characterised by an increase in collagen production, mucin production, and/or the number of fibroblasts in the dermis. These require to be differentiated, as there can be different associated systemic involvements and malignancies, and therefore varying treatment options and prognoses.

REFERENCES

1. Boin F, Hummers LK. Scleroderma-like fibrosing disorders. Rheum Dis Clin North Am 2008;34:199-220.
2. Kirsner RS, Pardes JB, Eaglestein WH, Falanga V. The clinical spectrum of lipodermatosclerosis. J Am Acad Dermatol 1993;28:623-7.
3. Holahan HM, Farah RS, Swick BL. Pretibial myxedema. Cutis 2014;94:60,73-4.

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