ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2016 October 26; 8(10): 559-622

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

A peer-reviewed, online, open-access journal of Cardiology

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2014-2017

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W J C

World Journal of
Cardiology

Contents

Monthly Volume 8 Number 10 October 26, 2016

DIAGNOSTIC ADVANCES

559 Remote electrocardiograph monitoring using a novel adhesive strip sensor: A pilot study

Bruce CJ, Ladewig DJ, Somers VK, Bennet KE, Burrichter S, Scott CG, Olson LJ, Friedman PA

MINIREVIEWS

566 Thoracic ultrasound: A complementary diagnostic tool in cardiology

Trovato GM

575 Physical activity in primary and secondary prevention of cardiovascular disease: Overview updated

Alves AJ, Viana JL, Cavalcante SL, Oliveira NL, Duarte JA, Mota J, Oliveira J, Ribeiro F

ORIGINAL ARTICLE

Basic Study

584 Impaired norepinephrine regulation of monocyte inflammatory cytokine balance in heart failure

Ng TMH, Toews ML

Retrospective Study

590 Left ventricular false tendons and electrocardiogram repolarization abnormalities in healthy young subjects

Lazarevic Z, Ciminelli E, Quaranta F, Sperandii F, Guerra E, Pigozzi F, Borrione P

596 Congenital coronary artery fistulas complicated with pulmonary hypertension: Analysis of 211 cases

Said SAM

Clinical Trials Study

606 Optimal C-arm angulation during transcatheter aortic valve replacement: Accuracy of a rotational C-arm computed tomography based three dimensional heart model

Veulemans V, Mollus S, Saalbach A, Pietsch M, Hellhammer K, Zeus T, Westenfeld R, Weese J, Kelm M, Balzer J

Randomized Controlled Trial

615 Randomized controlled trial of remote ischemic preconditioning and atrial fibrillation in patients undergoing cardiac surgery

Lotfi AS, Eftekhari H, Atreya AR, Kashikar A, Sivalingam SK, Giannoni M, Visintainer P, Engelman D

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WJC covers topics concerning arrhythmia, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, pediatrics, nursing, and health promotion. Priority publication will be given to articles concerning diagnosis and treatment of cardiology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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World Journal of Cardiology is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

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NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORIAL OFFICE
Xiu-Xia Song, Director
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World Journal of Cardiology
Baishideng Publishing Group Inc
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
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E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
October 26, 2016

INSTRUCTIONS TO AUTHORS
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World Journal of Cardiology

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4330/wjc.v8.i10.559

World J Cardiol 2016 October 26; 8(10): 559-565
ISSN 1949-8462 (online)

DIAGNOSTIC ADVANCES

Remote electrocardiograph monitoring using a novel adhesive strip sensor: A pilot study

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Conflict-of-interest statement: Mayo Clinic and Drs. Bruce Friedman Somers, Mr. Kevin Bennet and Scott Burrichter have a financial interest in technology referenced in this manuscript.

Manuscript source: Invited manuscript

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Received: February 19, 2016
Peer-review started: February 22, 2016
First decision: March 25, 2016
Revised: May 25, 2016
Accepted: July 29, 2016
Article in press: August 1, 2016
Published online: October 26, 2016

Abstract

The increase in health care costs is not sustainable and has heightened the need for innovative low cost effective strategies for delivering patient care. Remote monitoring holds great promise for preventing or shortening duration of hospitalization even while improving quality of care. We therefore conducted a proof of concept study to examine the quality of electrocardiograph (ECG) recordings obtained remotely and to test its potential utility in detecting harmful rhythms such as atrial fibrillation. We tested a novel adhesive strip ECG monitor and assessed the ECG quality in ambulatory individuals. 2630 ECG strips were analyzed and classified as: Sinus, atrial fibrillation (AF), indeterminate, or other. Four readers independently rated ECG quality: 0: Noise; 1: QRS complexes seen, but P-wave indeterminate; 2: QRS complexes seen, P-waves seen but poor quality; and 3: Clean QRS complexes and P-waves. The combined average rating was: Noise 12%; R-R, no P-wave 10%; R-R, no PR interval 18%; and R-R with PR interval 60% (if Sinus). If minimum diagnostic quality was a score of 1, 88% of strips were diagnostic. There was moderate to high agreement regarding quality (weighted Kappa statistic values; 0.58 to 0.76) and high level of agreement regarding ECG diagnosis (ICC = 0.93). A highly variable RR interval (HRV $\geqslant$ 7) predicted AF (AUC = 0.87). The monitor acquires and transmits diagnostic high quality ECG data and permits characterization of AF.

Key words: Remote; Electrocardiograph; Monitoring; Atrial fibrillation; Novel; Sensor

Core tip: The findings of this pilot study confirm that a remote monitoring system using a novel adhesive strip electrocardiograph (ECG) sensor can acquire and transmit diagnostic high quality ECG data over a period of 3 d when worn by elderly subjects leading active independent lives. Automated determination of heart rate variability permitted reliable characterization of ECG strips with atrial fibrillation. These data have implications for long term continuous monitoring for development of atrial fibrillation in independent elderly patients.

Bruce CJ, Ladewig DJ, Somers VK, Bennet KE, Burrichter S, Scott CG, Olson LJ, Friedman PA. Remote electrocardiograph monitoring using a novel adhesive strip sensor: A pilot study. *World J Cardiol* 2016; 8(10): 559-565 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i10/559.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i10.559

REMOTE ELECTROCARDIOGRAPH MONITORING USING A NOVEL ADHESIVE STRIP SENSOR: A PILOT STUDY

Due to increased longevity, people are facing an increasing prevalence of chronic disease that threatens their ability to live independently and has led to rapidly escalating healthcare costs. It is imperative that new, effective, economical and efficient methods to prevent and manage chronic disease are developed. Cardiovascular disease accounts for a significant burden of chronic illness, often manifesting as heart failure, and arrhythmias such as atrial fibrillation (AF) are commonly observed[1-4]. These arrhythmias may be difficult to detect, often initially presenting as decompensation of heart failure or stroke. Remote monitoring of physiologic measures such as the ECG and heart rate may provide an important option for early detection of cardiovascular compromise and arrhythmias[5]. Limitations of current monitoring systems include a large body burden and inconvenience in use, latency in transmission of physiologic information, enormous volumes of data for analysis consuming human resources, and significant false alarms generated by artifact, requiring human oversight[6-8].

We have developed a personal monitoring system capable of interfacing with additional low profile, unobtrusive, on-body and off-body sensors to provide real-time and cumulative data to a health care provider at any internet or cellular network enabled location. The system records ECG, respiration (*via* bioimpedance measurement), and physical activity using a 3-axis accelerometer. The system also has embedded algorithms that provide a self-diagnostic reliability index to qualify the value of the data, permitting reviewers to discard noisy signals, thus facilitating generation of alerts with greater specificity. In this pilot study, we sought to test the monitoring system in healthy volunteers residing in an independent living center, to determine whether the system satisfactorily acquires, stores, and displays ECG information of diagnostic quality in ambulatory, free-living individuals.

LITERATURE AND RESEARCH

We prospectively enrolled 10 healthy volunteers from residents of the Mayo Clinic Charter House, an assisted living center near the Mayo Clinic Rochester downtown campus. To be eligible, participants had to live in apartments with appropriate cellular network coverage. Subjects with implanted cardiac defibrillators or pacemakers were excluded.

After enrollment, a study coordinator provided each participant with a data hub that consisted of a SmartPhone preloaded with custom monitoring software (Google Nexus, HTC Corporation, Taipei, Taiwan), a charger for the SmartPhone, as well as two fully charged monitoring units and adhesive snap strips (Figure 1, BodyGuardian, Preventice Inc., Minneapolis, MN, described further below). A study coordinator instructed the subject on applying the adhesive strip sensor to the chest, methods for ensuring good signal quality, and how to ask for assistance if required.

Each subject was asked to use the system for 3 consecutive days. Supervised maneuvers, such as lying supine, sitting, standing, and walking were performed once per day, each day for 3 d, at which time the various signals were recorded. At the end of each 24-h period, the Study Coordinator exchanged the unit for a newly charged unit.

The study was approved by the Institutional Review Board. Since the system was not FDA approved at the time of the study, no clinical decisions or management changes were made based on data obtained during the trial.

REMOTE MONITORING SYSTEM

The remote health management system connects personal health sensors with secure mobile communication devices. The monitor front-end is composed of an electronic unit; an adhesive patch with attached electrodes and snaps for a rechargeable module. The rechargeable module measures 59 mm × 50 mm and houses the sensors, battery and wireless transmitter (Figure 2). It is detachable from the electrode snap strips to permit showering. The module is able to measure heart rate (HR), ECG, respiratory rate, and activity level.

Figure 1 Remote monitoring system. Top left: The rechargeable module is attached to the adhesive SnapStrip. The SnapStrip is positioned vertically over the sternum. Top right: The cellphone serves as (1) a wireless communication hub with the cloud and (2) as a user interface. Bottom: Recorded physiologic data including ECG and heart rate are presented on an iPAD for analysis and review. ECG: Electrocardiograph.

The ECG is recorded *via* the two inner electrodes (the distance between the inner electrodes is 70 mm and the distance between the outer electrodes is 104 mm). The electrode pads measure 10 mm diameter and have a signal sampling rate of 256 Hz with 12 bit resolution. Respirations are measured by injection of a low voltage charge from one pair of electrode contacts and measuring the change in voltage over a fixed distance on the other pair of electrode contacts (current amplitude: 100 μA, current frequency: 50 kHz, sampling frequency: 32 Hz). A three dimensional accelerometer acquires samples at 50 Hz and the signal is algorithmically processed to determine physical activity. Physiologic information is communicated to a remote server using a mobile phone as the communication hub. The mobile phone displays data acquisition, battery level and data transmission to the subject.

During normal operation, the system collects physiologic data and stores it in its on-board memory. The data are transmitted to the smart phone data hub at programmable intervals (nominally 60 min). In the absence of proximity to the data hub, data are stored on the rechargeable module attached to the adhesive strip until the next communication attempt. Data are automatically transmitted from the smart phone hub to a secure, HIPAA compliant server database.

Utilizing clinical algorithms, the system is capable of automated decision making based upon integration of data and can provide immediate feedback to the subject. The solution is a multi-tiered mobile health platform (Figure 3). The stored data are presented for review *via* a web-based interface, or using custom software on an iPad (Apple Computer, Cupertino, CA).

SELECTION OF ECG STRIPS FOR ANALYSIS

Each hour, a randomly selected two-minute ECG strip was automatically recorded and transmitted for the purposes of this study. Users could also manually activate a recording using the smart phone data hub interface.

ANALYSIS OF ECG QUALITY

Each of the ECG strips was read by 4 independent, experienced readers for ECG signal quality and rhythm interpretability. The readers were ECG technicians working in a 24-h continuous telemetry unit, and were blinded to clinical information and other readers' interpretations. Each reader independently rated the ECG quality using an ordinal scoring system: 0 Noise, cannot reliably determine QRS complexes 1 QRS complexes reliably seen and R-R intervals determined, but atrial activity indeterminate due to baseline noise 2, QRS intervals reliably recorded, and atrial activity seen but of poor quality, and PR interval not reliably seen 3, clean signal, with reliable assessment of QRS intervals, and PR intervals (when present). Quality scores were compared between each pair of readers and a weighted Kappa statistic was calculated assuming an ordinal outcome. In addition, in order to compare quality scores from all 4 readers, an intra-class correlation coefficient was calculated as a measure of agreement across all 4 raters.

ANALYSIS OF HEART RATE VARIABILITY

The system reports an average HR. The HR is derived by detecting the R wave component of the QRS complex for both normal and premature ventricular complexes (PVCs). The system calculates the interval between R waves (R-R interval) and processes this information to derive an average HR value every 10 s. The system also calculates heart rate variability (HRV). HRV is a value derived from the variance of the ECG R-to-R intervals based on a 10-s time interval. It is sensitive to both normal beats and PVCs. An event is triggered when the number of heart beats per minute varies by more than the HRV threshold. For example, if the threshold is set

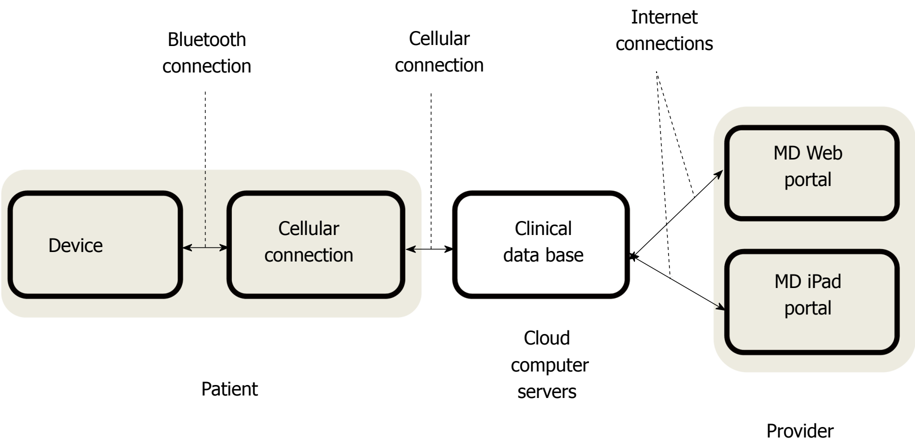

Figure 2 Remote monitoring system architecture.

Figure 3 Representative examples of electrocardiograph strips. A: This strip demonstrates sinus rhythm. All 4 raters scored this strip as having high quality (score 3); B: This strip demonstrates atrial fibrillation. Although the raters quality score ranged from 1 through 3, the irregularly irregular RR interval and absence of discernible P waves present in this Electrocardiograph signal is diagnostic for atrial fibrillation.

to 30-bpm, a HR that varies from the average by more than 5 beats in a 10 s interval triggers an HRV event. Use of the HRV threshold to trigger an event helps to identify ECG tracings that may require physician review as they are more likely to indicate arrhythmia, based on dropped beats or irregular rhythm or increased heart rate. Logistic regression analysis was used to examine the association of HRV with the outcome of AF. A Receiver Operator Characteristic curve and concordance statistic (AUC) was used to illustrate the sensitivity and specificity of HRV.

RESULTS OF STUDY

Ten healthy volunteers were recruited to the study (4 men, average age 79.5 years (range 74 to 92 years). All 10 subjects wore the device for 72 h. Data from all 10 subjects were stored and were available for analysis for the 72-h duration the device was used.

Assessment of ECG quality

Data for 2630 ECG 2-min strips were available for analysis. Rhythm was classified by each of the 4 readers as sinus, AF, indeterminate or other (Table 1). There was moderate agreement in rhythm classification between pairs of readers (median Kappa = 0.65). In particular, variability was noted in the percentages of strips rated by each reader as sinus (48%-70%) while the percentages of those rated as AF was comparable across readers (11%-15%). Quality scores were compared between each pair of readers. There was a moderate to high level of concordance between readers (weighted Kappa statistic values ranged from 0.58 to 0.76). There was also a very high level of agreement across the 4 readers (ICC = 0.93).

The combined average rating of ECG quality based

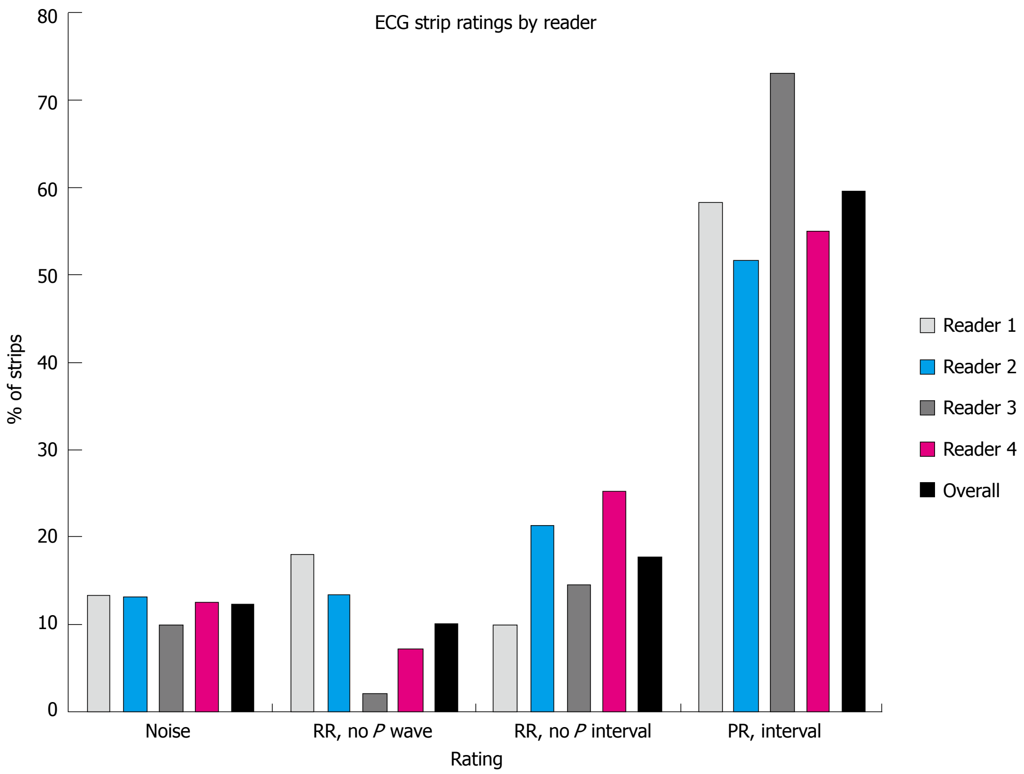

Figure 4 Electrocardiograph strip ratings by reader. Average combined and individual assessments of electrocardiograph quality based on 4 independent experienced raters. The vertical axis represents the percentage of strips rated within each category for each reader. ECG: Electrocardiograph.

Table 1 Electrocardiograph rhythm classification by reader

Rhythm	Reader 1 *n* (%)	Reader 2 *n* (%)	Reader 3 *n* (%)	Reader 4 *n* (%)
Sinus	1790 (68%)	1247 (48%)	1833 (70%)	1366 (52%)
AF	292 (11%)	384 (15%)	294 (11%)	334 (13%)
Indeterminate	457 (17%)	974 (37%)	497 (19%)	773 (29%)
Other	88 (3%)	4 (0.1%)	3 (0.1%)	154 (6%)

AF: Atrial fibrillation.

on the 4 independent raters was: No RR-noise 12%, RR-no P-wave 10%, RR-no PR interval 18%, PR interval 60% (if in sinus rhythm). Thus, if a minimum diagnostic quality was determination of an RR interval, 88% of strips were sufficiently diagnostic to provide a determination of HR, and a minority of strips was considered noise related to artifact (12%). Examples of ECG strips and the combined and individual assessments of ECG quality are presented in Figures 3 and 4.

One of the 10 subjects had persistent AF. In order to preliminarily assess the utility of HRV for identifying AF, and because of the variability in ECG classification variability, analysis was performed on those strips that were found to be in agreement across all 4 readers as either sinus rhythm (n = 889) or AF (n = 252). HRV scores were found to be significantly different between those classified as Sinus Rhythm (mean = 10.0, SD = 2.4) and those classified as AF (mean = 4.7, SD = 5.9), P < 0.001. Based on this finding, we defined images with a variability score of 7 or greater as highly variable. Ninety-seven percent of the strips with HRV ≥ 7 were classified as AF. This variable was also entered into a logistic regression model for predicting AF. The univariate area under the curve (AUC) for a highly variable RR interval (HRV ≥ 7) in predicting AF was 0.87 (Figure 5). Using HRV ≥ 7, sensitivity was calculated to be 97% (95%CI: 94-99) while specificity was 77% (74-80), positive predictive value was 54% (49-59) and negative predictive value was 99% (98-99).

DISCUSSION

The findings of this pilot study demonstrate for the first time the ability of this low body burden, unobtrusive, wireless remote monitoring system to acquire and transmit high diagnostic quality ECG data when worn by elderly subjects leading active independent lives, outside of a hospital environment. Artifact in ambulatory 24/7 ECG recordings results in erroneous arrhythmia classification that may significantly and adversely affect diagnostic accuracy and hence quality of care. These artifacts result from myopotentials (most commonly from the pectoralis muscles), galvanic skin currents, and less commonly electromagnetic interference. These issues are particularly prevalent in ambulatory settings and Band-Aid style sensors with only two electrodes are particularly at risk. Thus, it is reassuring that most of the ECG recordings using this system provided clinically diagnostic information, free from artifact. Furthermore, although the study was not designed to assess arrhythmia detection, serendipitously, one subject had persistent atrial fibrillation. Analysis of segments using the HRV

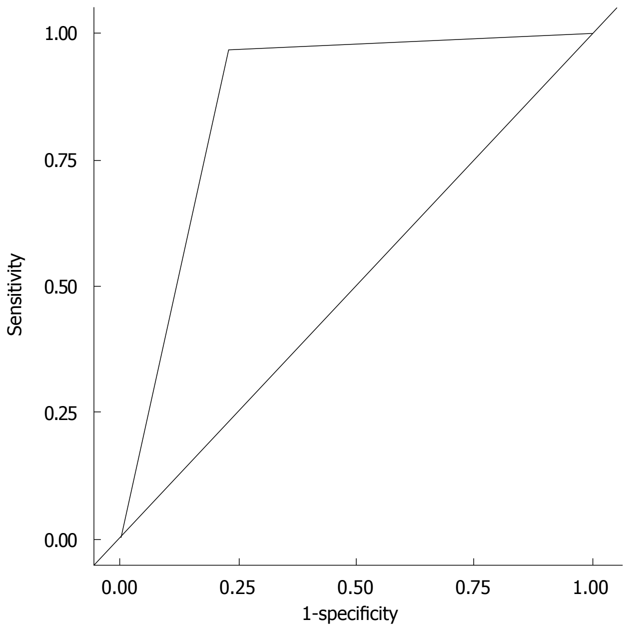

Figure 5 Receiver operator characteristic curve for atrial fibrillation using heart rate variability ≥ 7.

algorithm permitted differentiation of ECG strips with AF from SR.

Determining reliable high quality ECG recordings is important in ambulatory monitoring systems to ensure appropriate diagnosis. It is also important to be able to characterize poor quality ECG data or noise (artifact) so that these data can be ignored. This is particularly important when large amounts of data are being recorded over prolonged periods, when frequent false alarms generate both user and healthcare provider "alarm" fatigue rendering the system cumbersome, and consequently adversely affecting effectiveness, adherence and prescription. The monitor system is capable of acquiring high quality ECG recordings using an unobtrusive adhesive electrode sensor in an ambulatory setting.

HRV as defined by this system may be useful for detection of arrhythmias such as atrial fibrillation. Indeed, in this study, one subject had AF. When excessive HRV was noted, ECG data strips from the patient could be reliably determined. This observation could be potentially useful in detecting AF, particularly if new AF develops in an individual who was previously in sinus rhythm (when HRV would be low). High HRV may be seen with arrhythmias other than AF, such as frequent PVC's.

LIMITATIONS

This study has limitations that may constrain broad generalization of our findings. The subjects enrolled in this study were elderly residents of an assisted living facility ranging in age from 72 years to 92 years. They are thus not representative of other population groups who may be younger, more active or less healthy. Furthermore, although there were large amounts of data for analysis, the subject sample size was small. The study design requirement for visual confirmation of rhythm and ECG quality rather than relying on automated algorithms made it necessary to limit the number of subjects studied. In mitigation, more than 2600 rhythm strips from the 10 subjects were visually inspected by study investigators to ascertain cardiac rhythm, which was labor and time-intensive. To prove the clinical utility of this approach in the future will require studies with larger numbers of subjects, which will only be practical with systems capable of automated rhythm identification in order to enable scalability. Additionally, very few patients experienced an arrhythmia (atrial fibrillation), and patients with other arrhythmias were not included. However, this was a pilot study directed toward evaluating the ergonomics, tolerability, and effectiveness of continuous EKG monitoring, and to determine whether the quality of the EKG recording could be preserved over extended periods.

CONCLUSION

The findings of this pilot study confirm that a remote monitoring system using a novel adhesive strip ECG sensor can acquire and transmit diagnostic high quality ECG data over a period of 3 d when worn by elderly subjects leading active independent lives. Automated determination of heart rate variability permitted reliable characterization of ECG strips with AF.

ACKNOWLEDGMENTS

We would like to thank Bridgette A. Wagner and DeJae Ladewig for assistance in preparing the manuscript.

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World Journal of Cardiology

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DOI: 10.4330/wjc.v8.i10.566

World J Cardiol 2016 October 26; 8(10): 566-574
ISSN 1949-8462 (online)

MINIREVIEWS

Thoracic ultrasound: A complementary diagnostic tool in cardiology

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Author contributions: The minireviews was written by the author stated.

Conflict-of-interest statement: No conflict of interest is declared in this invited editorial manuscript.

Manuscript source: Invited manuscript

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Received: March 17, 2016
Peer-review started: March 19, 2016
First decision: April 19, 2016
Revised: May 20, 2016
Accepted: July 29, 2016
Article in press: August 1, 2016
Published online: October 26, 2016

Abstract

Clinical assessment and workup of patients referred to cardiologists may need an extension to chest disease. This requires more in-depth examination of respiratory co-morbidities due to uncertainty or severity of the clinical presentation. The filter and integration of ecg and echocardiographic information, addressing to the clues of right ventricular impairment, pulmonary embolism and pulmonary hypertension, and other less frequent conditions, such as congenital, inherited and systemic disease, usually allow more timely diagnosis and therapeutic choice. The concurrent use of thoracic ultrasound (TUS) is important, because, despite the evidence of the strict links between cardiac and respiratory medicine, heart and chest US imaging approaches are still separated. Actually, available expertise, knowledge, skills and training and equipment's suitability are not equally fitting for heart or lung examination and not always already accessible in the same room or facility. Echocardiography is useful for study and monitoring of several respiratory conditions and even detection, so that this is nowadays an established functional complementary tool in pulmonary fibrosis and diffuse interstitial disease diagnosis and monitoring. Extending the approach of the cardiologist to lung and pleura will allow the achievement of information on pleural effusion, even minimal, lung consolidation and pneumothorax. Electrocardiography, pulse oximetry and US equipment are the friendly extension of the physical examination, if their use relies on adequate knowledge and training and on appropriate setting of efficient and working machines. Lacking these premises, overshadowing or misleading artefacts may impair the usefulness of TUS as an imaging procedure.

Key words: Thoracic ultrasound; Echocardiography; Congestive heart failure; Pneumonia; Pleural effusion; Cancer; Pneumothorax; Clinical risk management

Core tip: Thoracic ultrasound (TUS) is an imaging tool, well developed but not uniformly used, which provides information on pleura, lung and heart disease; TUS is a procedure that deserves greater dissemination, since quite neglected by cardiologists, pneumologists and even radiologists in the current practice; small pleural effusions (useful for monitoring congestive heart failure), lung consolidation (particularly relevant in pneumonia) and pneumothorax, even with different reliability, may be detected; adequate training, avoiding overshadowing or misleading artefacts, is needed and must be integrated within curricula.

Trovato GM. Thoracic ultrasound: A complementary diagnostic tool in cardiology. *World J Cardiol* 2016; 8(10): 566-574 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i10/566.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i10.566

OVERVIEW

This brief overview is essentially medical-centred, in a dual sense: (1) it regards the clinical approach (obviously patient-centred in its scope and ethics) that is, and must be, driven by an individual medical doctor with the most comprehensive as possible skills and expertise; and (2) it regards the clinical innovation and research, which raised and raise from the observation and reasoning of single clinicians; the dissemination of skills, practice, recommendation and guidelines must have the support of the best available clinical evidences, with the feature of appropriateness, sustainability and cost-benefit for the patient and the community.

This is particularly true for a procedure, such as thoracic ultrasound (TUS), basic, if not elementary, quite neglected by the cardiologist. This despite TUS was early concurrently practised with echocardiography[1] and, subsequently, limitedly used by internists, radiologists and in paediatrics[2-9].

The requirement that TUS shares with echocardiography[10] are remarkable. The effort of a good quality imaging, the reproducibility of the procedure by different operators and equipments and the criteria of the indications[9] can be summarized in two sentences: (1) the use of TUS for initial diagnosis is recommended when there is a change in the patient's clinical status, likely related to pulmonary function; and (2) when new data from a TUS would result in the physician changing the patient's care.

There is an established agreement for these criteria in cardiological patients for their use in echocardiography[9,10]. Moreover, alike echocardiography, TUS is not recommended as routine testing equally when the patient has no modification in clinical status or when a physician is unlikely to change care for the patient based on the results of testing: These are both two strongly advised points against the use of echocardiography as a routine testing, which are suitable to be transferred also to TUS[9].

Differently from echocardiography, TUS is almost exclusively an imaging tool, without any "functional" application comparable to M- B- and Doppler Echocardiography, no accurate and reproducible dynamic measures, no translational relevance in the description and interpretation of mechanisms of disease[11].

Nonetheless, the knowledge of these limitations and the use of the few direct information provided by TUS are a substantial add-on to the clinical strategy of the cardiologist[12], also in emergency[13-15].

RATIONALE AND KEY POINTS

The customized rules of a journal presentation are: What, who, why, when, where, how.

What

Clinical assessment and workup of patients referred to cardiologists is a task often more comprehensive and not only focused on the heart since it is extended to chest disease. This approach may require more in-depth examination of respiratory co-morbidities due to uncertainty or severity of the clinical presentation.

Who

The cardiologist, facing respiratory associated symptoms and co-morbidities, can usually detect and manage the clinical presentation by physical examination, a thoroughly collected story, and using the current non-invasive procedures at the hands. The cardiologist's view is of paramount relevance for the clinical reasoning and action of the other specialists. The adjunct of TUS examination is an excellent companion to the other knowledge, procedures and skills.

Why

According to uncertainty or severity of the clinical presentation, the referral to radiologist and to pneumologist is an assignment that is more appropriate if explicitly addressed with objective information, which exclusively can produce evident cost-benefit advantages[16,17]. Some investigation implicitly aims to a clinical risk management analysis with subsequent recommendations. Actually, TUS can be an excellent risk-reducing tool by increasing: (1) diagnostic certainty; (2) shortening time to definitive therapy; and (3) decreasing complications from blind procedures that carry an inherent level of complications. The background and the backbone of it all is an efficient network of timely, coordinated and experienced professionals, and the analysis of obstacles and structural barriers that may take place or that are interposed[17,18].

When

The contribution of the cardiologist in the diagnosis and management of respiratory disease must be well timed. Apart the obvious clinical judgement, the expert task of filtering ecg and echocardiographic information, addressing to the clues of right ventricular impairment, pulmonary embolism and pulmonary hypertension, and other less frequent conditions, including congenital, inherited and systemic disease, is an help for timely diagnosis and therapeutic choice. Even with limited indications, the concurrent use of TUS by the cardiologist is important in this regard.

Where

Despite the evidence of the strict links between cardiac and respiratory medicine, the two ultrasound imaging approaches to heart and chest are still separated. This is due to different skills of physicians, to the different preference of patients in the choice of type of referrals and even due to the suitability of equipments and probes, which are not equally fitting for heart or lung examination and not always already available in the same room or facility.

How

Several respiratory conditions are currently studied and monitored, when not preliminary detected, by echocardiography, which is nowadays an established tool in the workup of pulmonary fibrosis and diffuse interstitial disease. As a further step, the ultrasound (US) approach of the cardiologist should be extended to lung and pleura, achieving simple and straightforward information suitable of articulation within the clinical cardiology frame. Electrocardiography, pulse oximetry and US equipment are the friendly technological extension of the physical examination, if their use is based on adequate knowledge and training of the professionals, on appropriate setting of tools which must be efficient and well working. If these premises lack, overshadowing or misleading artefacts can ensue: Overall, the procedure must be affordable, reliable and comfortable for both the patient and the well-trained doctor[18-20].

CHEST ULTRASOUND: THE THORAX, THE LUNG, THE HEART

Many clinical subsets increasingly use chest ultrasound, *i.e.,* TUS procedures. This is due to the greater availability of portable point-of-care US equipment, suitable also at the patient's bedside, in the ward, in the emergency and intensive care unit, in outpatient clinics and even at home of the patients themselves.

TUS procedure allows the view of the most superficial parts of the chest: The thorax "wall", the pleura, which may be a virtual space or a real fluid-filled space in pleural effusion, or may be a mass-occupied space in many cancers, and the lung itself[9]. Some part of the lung, where not overshadowed by ribs or other bones, such as scapula, is therefore clearly visible only if "consolidated". This happens in atelectasis, pneumonia and cancer, provided that the mass or nodule strictly adheres close to pleura, becoming accessible to micro-invasive procedures[21-23]. There is no TUS established criterion for differentiating the nature of lung consolidation. Physical interaction of the ultrasonic beam at the tissue/air interface strongly influences or frankly impairs transthoracic US imaging, so that TUS cannot detect any mass or nodule, behind more superficial and even small portion of aerated lung, often even clearly defined by radiological procedures.

The heart is one of the organ visible by ultrasound in the thorax - by echocardiography - and, as it is well known, also for this reason the worst enemy of its imaging is the air, the pulmonary air; as a consequence, any cardiologist focuses on the detection of the acoustical windows for achieving and recording useful and better images and videos. Actually, in children and in thin persons, high frequency (6-10 MHz) linear or convex probes[9] enhance the view of the chest wall and of the pleura-lung abnormalities. This is possible because, and only if the structures we are attempting to see are just below our transducers. The yield of a sector or phased array probe is usually more limited; the only notable exception is the detection, also by sector probes, of pleural fluid, which sometimes may be well visible even anteriorly, sometimes not well differentiated by a pericardial effusion requiring a complete lateral and posterior chest assessment by TUS[24]. More easily and with a greater sensibility for small amounts of fluid is the view through a window in the lateral and posterior part of the chest, better with the patient upright or sitting[9].

A LONG STORY: PIONEERS AND CURRENT USERS

TUS is a complementary tool also in cardiology[25-30], along its main use for more specific pleura and lung disease[31-34]. Nonetheless, TUS pioneering and practice began in late 60's. Then, the most important B-mode studies concurrently, in the same centre in United States, demonstrated the usefulness of TUS, along with the assessment of mitral and tricuspid valve disease[35,36], for the diagnosis of lung consolidation, envisaging an help even in pulmonary embolism[37]. In early 70's, with the improved quality and greater availability of the US equipments, the use of TUS as an allied support of cardiologists performing echocardiography was recognized and practised. Our practice was done, regretfully, without delivering relevant cardiology publications on this topic, which was considered a parallel but minor informative practice. Thereafter, in late 80's in France[5], the TUS procedure was optimally developed by pneumologists, as it was in Germany[6-8], and in Italy[3] defining appropriately the criteria of pneumothorax and of lung consolidation. The clinical research and practice of TUS in cardiology in late 90's in Japan, demonstrated the usefulness of detecting and monitoring pleura effusions[25-28,30], an achievement that others subsequently confirmed[29] enhancing the dissemination of knowledge and interest for TUS in Cardiology. The use in pediatric and newborn intensive care facilities was[2,4] and still is[17,38,39] greatly developed with the contribution of pediatric radiologists. The main barriers to the dissemination of an appropriate TUS practice are the limited availability of clinical application studies within cardiology and pneumology departments, the lack of TUS curricula inside those residency pro-

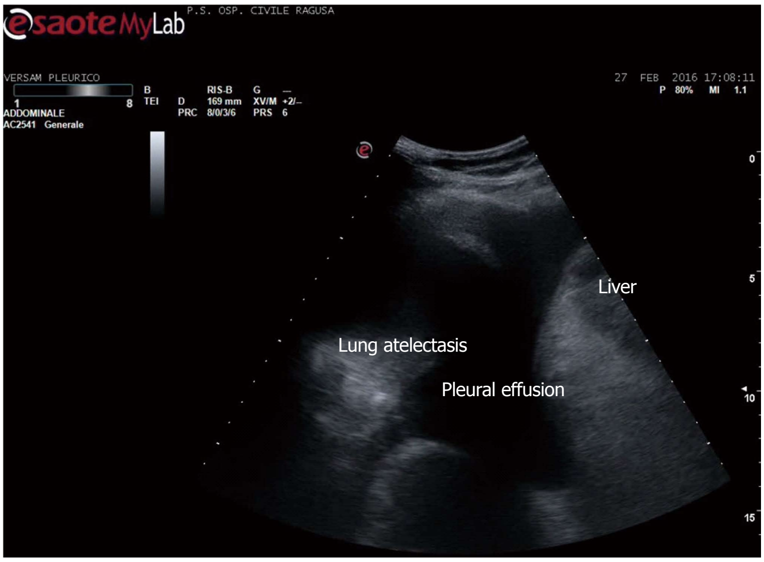

Figure 1 Pleural effusion.

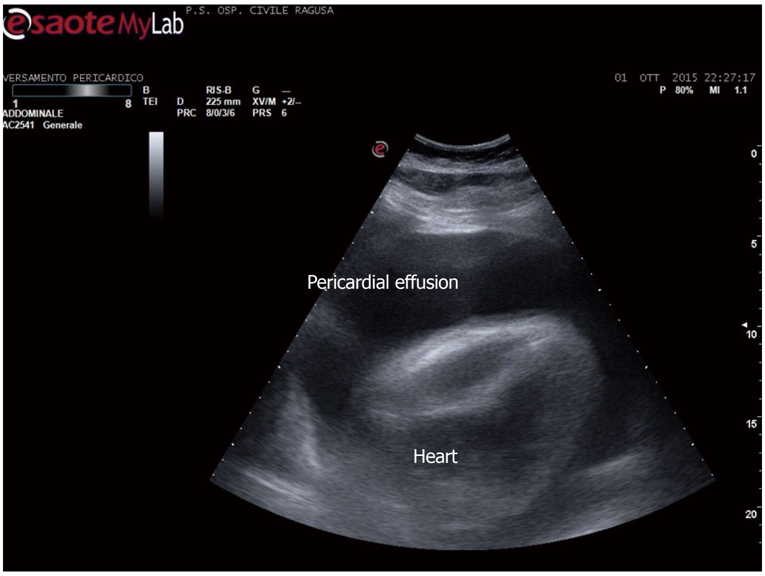

Figure 2 Pericardial and pleural effusion.

grams[18-20] and the small attention devoted to research and publications in this field by cardiologists.

THE PROCEDURE: NEEDS, FACILITIES, COLLABORATION AND INDICATIONS

There are good reasons for which a cardiologist should seek for the contribution of TUS, and they stems from the referral for a clinical consultation that usually includes echocardiography.

Apart the itemization of the main indications and conditions in which TUS can be of help for the diagnosis and workup of patients, which is below detailed, the focus of the cardiologist performing TUS is clinically-driven by the two more important concurrent conditions: (1) pleural effusion (Figure 1), which is observed even better by video-clip and may be associated with pericardial effusion (Figure 2); (2) lung consolidation (Figure 3) which may be due to pneumonia, as in this case, but which needs a further radiological work-up if there is the suspicion of cancer or lung atelectasis; (3) the appearance of B-lines is a very generic clue (Figure 4), particularly because their count is at best impractical and imprecise, as it is obvious looking at any videoclip; (4) differently, the dynamic view of the disappearance of pleura sliding (Figure 5) is a very specific sign, unless it is observed in the apical part of the lung, where it can be often undetectable for anatomical reasons; however, detection of the absence of pleura sliding is not a very usual need to search for a cardiologists.

The cardiologist can perform TUS procedure, after an appropriate training and with the adequate probe implementation of the US equipment, executing an articulated heart-lung US approach.

A list of the main findings attainable by TUS: (1) small or huge pleural effusions. These can be associated with pericardial effusion, and can be isolated pleural fluid effusions, unilateral, bilateral or, as less frequently happens, loculated. If loculated, effusions

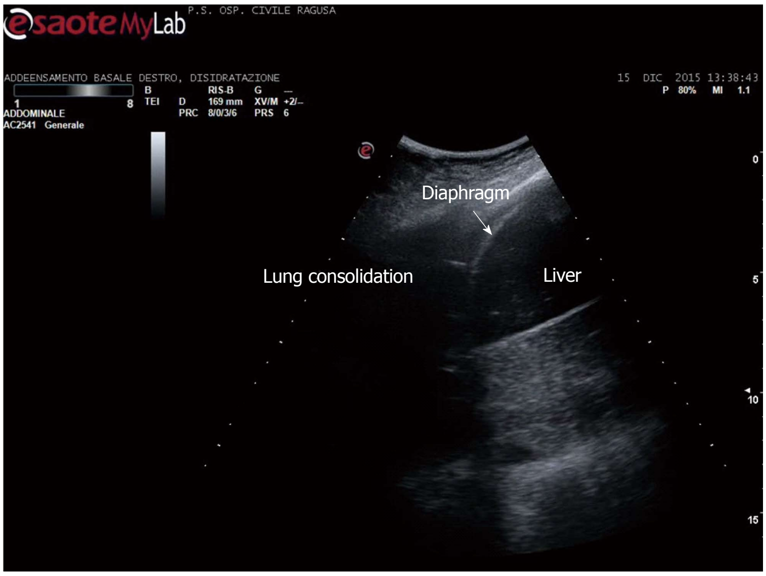

Figure 3 Lung consolidation. Community acquired pneumonia in an adult.

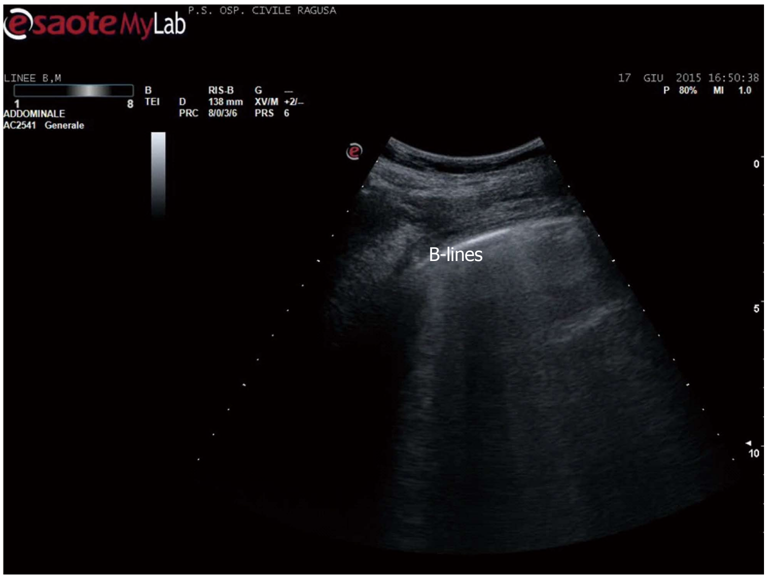

Figure 4 B-lines in acute heart failure. B-lines count is a dynamic observation, essentially qualitative, since the number changes continuously - from 3 to 6 or more - in case of numerous b-lines. Identical artefacts are detectable in other conditions, including pulmonary fibrosis and dyspnoea due to other causes, including BPCO.

may be not detected in the lower part of the chest, but only at the level where the fluid is actually restricted. The sensibility of linear *vs* phased array probes is greater (100% *vs* 91%) for uncovering pleural effusions; both are more sensible in comparison with chest X-rays[24]; (2) the recognition of pleural effusion is a frequent occurrence in echocardiography out-patient consultations, and follows referrals for dyspnea, due to congestive heart failure and/or respiratory failure; valvular or congenital heart disease; ischemic or primary myocardial heart disease; cancer disease, primitive or metastatic; other conditions.

These last miscellanea should be considered a particularly relevant group, since the detection of not previously suspected pleural-pericardial effusion can be the first evidence of otherwise still non-identified disease, or a clue of greater severity of an already diagnosed disease.

We see in the current practice pleural effusions, often previously undetected, in: Hypothyroidism; rheumatic and auto-immune disease; malnutrition, due to dietary insufficient intake, to intestinal disease (such as coeliac disease) and to liver disease; nephrosis.

The small, quick diagnostic step of the cardiologist can open the road for a more effective diagnosis and treatment of several patients in these cases.

A journey of a thousand miles starts under one's feet (Lao-Tzu)

The detection and monitoring of pleural effusion was the object of very careful studies, which demonstrated the usefulness of the detection and of the monitoring of pleural effusion in congestive heart failure patients throughout the time-course of management outcome[25-29] and along ecg changes[30].

Pleura-lung consolidation

This is a more detailed imaging diagnosis, non-specific and not suitable for reliably identifying the cause. It can address to subpleural pneumonia areas[31], pleural

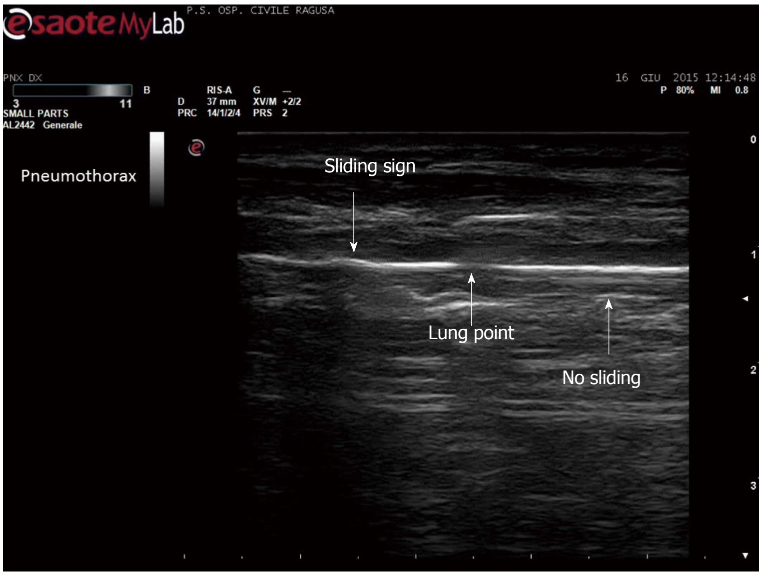

Figure 5 Disappearance of pleural sliding, better demonstrated by video. Which is here showed as a drop in the continuity of the line, not moving side by side (by courtesy of Giuseppe Molino, MD, MCAU Ospedale Civile di Ragusa, Italy).

and/or subpleural nodes[32], atelectasis[33] and loculated-organized pleural effusions[34], without a definite differentiation[9].

This type of report needs a very systematic chest examination, which should not be, usually, a part of the cardiological US procedure, requires more appropriate probes (linear or convex), and a great level of suspicion, apart the skills and a lasting expertise.

Nonetheless, there are several good reason for performing this type of TUS examination, in selected patients, along the echocardiographic examination, when a consolidation is suspected[35-37], if the cardiologist has achieved a reasonable level of skills, expertise and training: (1) newborn and children with fever, even without overt severe respiratory distress[38,39]. In these small patients, the chest X-ray is usually postponed after having achieved the physical examination evidence of pulmonary involvement and, in the recent years, after some evidence at physical examination of TUS subpleural consolidation, particularly if associated with small pleural effusion; (2) adults with respiratory symptoms, with or without fever, particularly in the outbreaks of community pneumonia[40]. Both situations can be associated with previous or active endocarditis, so that this diagnostic step can be useful for completing the elements of the clinical reasoning of the cardiologist; (3) adults with evidence of small pleural effusion without a definite suspicion of pulmonary infection and with the possibility of lung cancer. This is a special case, usually behind the actual skills and expertise of any US professional. Nonetheless, if positive, TUS could hasten the prescription of more efficient imaging (CT or NMR); and (4) pleural line thickening. This is a minor but relevant clue, detected in several diffuse pulmonary interstitial disease[41] and in conditions such as asbestosis[21,42,43]. This can be an early sign of involvement or of worsening of an already known disease, and can help in the decisional tree for the prescription of a radiological examination - CT.

TUS clues of pneumothorax: This is an important application, even without specific criteria, useful in emergency, for the diagnosis of spontaneous or traumatic/post-procedural pneumothorax, particularly in conditions of limited medical resources. TUS diagnosis relies on the sign of the absence of sliding on the pleural view[44,45] and to other less specific signs[9]. With the considerable exception of unavailability of adequate roentgenologic facilities, the TUS diagnosis is a preliminary step to the urgent definition and demonstration - usually by CT - of the chest condition, amenable to the choice of the most appropriate management[46,47].

ABSENCE OF TUS IMAGING

The ring-down artefacts in patients with dyspnea

In patients with severe dyspnea, whatever the cause (pulmonary oedema, congestive heart failure with or without orthopnea, pulmonary fibrosis, and other conditions), the so-called B-lines artifacts[48-53], which prevents the vision of lungs with the remarkable exception of pleural effusion, may overshadow an adequate imaging. Indeed, the clinical reliability of B-lines count is a doubtful stand-alone criterion, particularly because "in patients with a moderate to high pretest probability for acute pulmonary oedema, an US study showing B-lines can be used mainly to strengthen an emergency physician's working diagnosis of acute pulmonary oedema. In patients with a low pretest probability for acute pulmonary oedema, a negative US study can almost exclude the possibility of acute pulmonary oedema"[54]. These are the conclusion of the most accurate metanalysis on this topic, which substantially asserts that the only information provided by the B-lines artifacts is that one already available on clinical basis. Moreover, over-reliance on such tools could undermine quick clinical decisions in emergency scenarios[55]. Acute severe dyspnea due to causes other than pulmonary oedema, including exacerbation of chronic obstructive pulmonary disease and pulmonary fibrosis, presents with the same B-line profile as acute pulmonary oedema. It is therefore obvious that in a clinical scenario of severe dyspnea, preliminary diagnosis by history and clinical examination takes precedence, and, in fact, it is almost all that the physician and the patient need for effective intervention. Finally yet importantly, the fact that the number and evidence of B-lines is greater according to the age of the patients[56], not to the body size[57], more than to other factors raises further doubts on a realistic use of this criterion for "universal" clinical purposes, as sometimes claimed.

Indeed, the reference tool in acute pulmonary oedema is auscultation, and the level on the chest - basal, middle, and apical - where wet sounds are heard[9]. Most source articles dealing with the B-lines approach do not mention such features and do not mention in the reports the extension of lung involvement. Furthermore, those articles also fail to inform us of the ultrasound time course of the observed pulmonary oedema cases, from the onset to improvement or recovery, or to the worsening of the clinical situation. This is a crucial point. Differently, usefulness of reduction of TUS pleural effusion with clinical improvement is a very well demonstrated and practised approach since several years[9,24-28]. Nonetheless, the reduction of artefacts grossly runs in parallel with the improvement of dyspnea, whatever is the prominent cause, allowing a grossly graded US detection of pleura-lung abnormalities, if any. The prominent role even in emergency of echocardiography over TUS is, also nowadays[58], when still necessary, confirmed again[15]. Unfortunately, TUS does not provide a substantial adjunctive contribution for the diagnosis of pulmonary embolism[59], as hopeful[37].

TUS guidance for intervention procedure

This is probably the most important application of TUS, useful for diagnostic of nodules by fine needle aspirate biopsy, for diagnosis and drainage treatment of pleural-pericardial effusions and, rarely, of cysts, for the guidance toward chest vessels[60] and, in special cases, toward the diaphragm[61]. The role of the cardiologist in these very specific actions is almost null; nonetheless, a trans-thoracic approach of pericardial effusions[62], instead of sub-xiphoid as currently usual, is safe and in some case - abdominal surgery or trauma - the best suited. The use of probes with a central hole - convex or linear - is particularly useful because these probes allow a greater precision in the guidance and in the visual tracing of the needle toward its target[9,16,21,22,63]. The percentage of complications is minimal or absent.

The cardiologist: The culture and the methodology

After its beginning and development in the cardiology and in the radiology units, TUS was quite relegated, if not neglected. It was used mainly in contexts of limited resources, when there was the need of quick diagnosis and, in a very privileged niche, in the laboratories of interventional diagnostic ultrasound, for performing highly focused and precise lung, nodes and pleural biopsies or therapeutical procedures.

The culture of the cardiologists and of the radiologists has the key traits of addressing quality and conformity to the morphology of the US images, of investigating using unambiguous criteria of comparisons between measurements (invasive, non-invasive, anatomic) and of achieving not redundant, not time wasting and not potentially misleading information. With these criteria in mind, the contribution of TUS, apparently limited to a couple of items and information, is, in the hands of the cardiologist performing echocardiography, a valuable add-on for ruling-in or ruling-out pleural effusions. Overall, the cardiologist may detect isolated lung consolidations, possible pneumonia or other masses, and pleural line thickening, as a possible clue of interstitial lung disease. The available information, particularly in point of care ultrasound, suffers from several limitations which were optimally addressed somewhere else: The concept of a focused examination implies that one is addressing binary questions (*e.g.,* does the patient have cholecystitis or not?). In practice, many diagnoses require the assessment of a variety of imaging findings of varying subtlety and often deal in probabilities rather than binary assessments. Lastly, in order to assess the quality and validity of point-of-care ultrasonography and to permit its correlation with other imaging methods, it is essential that images be documented, ideally on the same picture archiving and communication system used for other imaging[64]. It should be strongly considered that "it is not time to mandate training in the performance of lung ultrasound without proving that ultrasound can reliably make an accurate diagnosis"[65]; moreover, "formal training incorporating ultrasound in adequate curricula is crucial for physicians, avoiding simplistic numeric rules, since medicine is not arithmetic"[66]. The trends of contemporary practice and research address to precision, but also to sustainability within a framework of predictive, preventive and personalized medicine and an affordable implementation of clinical risk assessment and management planning[67-70]. TUS is a significant complementary aspect of this strategy, which can be integrated and articulated within the daily work of the cardiologist.

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P- Reviewer: Al-Mohammad A, De Ponti R, Peteiro J, Simkhovich BZ
S- Editor: Qiu S **L- Editor**: A **E- Editor**: Wu HL

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4330/wjc.v8.i10.575

World J Cardiol 2016 October 26; 8(10): 575-583
ISSN 1949-8462 (online)

MINIREVIEWS

Physical activity in primary and secondary prevention of cardiovascular disease: Overview updated

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Author contributions: Alves AJ contributed to writing and reviewing the literature; Viana JL, Cavalcante SL, Oliveira NL, Duarte JA, Mota J and Oliveira J contribute to design and writing; Ribeiro F provided overall study supervision.

Conflict-of-interest statement: Alberto J Alves and others authors declare no conflict of interest related to this publication.

Manuscript source: Invited manuscript

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Received: June 16, 2016
Peer-review started: June 17, 2016
First decision: July 4, 2016
Revised: July 14, 2016
Accepted: August 17, 2016
Article in press: August 18, 2016
Published online: October 26, 2016

Abstract

Although the observed progress in the cardiovascular disease treatment, the incidence of new and recurrent coronary artery disease remains elevated and constitutes the leading cause of death in the developed countries. Three-quarters of deaths due to cardiovascular diseases could be prevented with adequate changes in lifestyle, including increased daily physical activity. New evidence confirms that there is an inverse dose-response relationship between physical activity and cardiovascular disease and mortality risk. However, participation in moderate to vigorous physical activity may not fully attenuate the independent effect of sedentary activities on increased risk for cardiovascular diseases. Physical activity also plays an important role in secondary prevention of cardiovascular diseases by reducing the impact of the disease, slowing its progress and preventing recurrence. Nonetheless, most of eligible cardiovascular patients still do not benefit from secondary prevention/cardiac rehabilitation programs. The present review draws attention to the importance of physical activity in the primary and secondary prevention of cardiovascular diseases. It also addresses the mechanisms by which physical activity and regular exercise can improve cardiovascular health and reduce the burden of the disease.

Key words: Physical activity; Primary prevention; Secondary prevention; Cardiovascular disease; Health care evaluation mechanisms

Core tip: This review describes the benefits of physical activity in primary and secondary prevention of cardiovascular disease. Physical inactivity is related to high blood cholesterol and accumulation of visceral fat, accompanied by low-grade vascular inflammation, which in turn is associated with insulin resistance and atherosclerosis leading to the development of coronary artery disease. In contrast, physical activity decreases vascular inflammation, and improves endothelial function and coronary circulation, preventing myocardial ischemia. Health professionals and policy makers in public health should align strategies to increase participation in physical activity.

Alves AJ, Viana JL, Cavalcante SL, Oliveira NL, Duarte JA, Mota J, Oliveira J, Ribeiro F. Physical activity in primary and secondary prevention of cardiovascular disease: Overview updated. *World J Cardiol* 2016; 8(10): 575-583 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i10/575.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i10.575

INTRODUCTION

Notable progresses have been observed in the treatment of cardiovascular disease. Hence, cardiovascular mortality faced a progressive decline in the past two decades. Despite these progresses, incidence of new and recurrent coronary artery disease (CAD) remains elevated[1] and constitutes the leading cause of death in the developed countries[2]. This is expected to increase health care costs, increase work disability and reduce quality of life[3].

Development of cardiovascular diseases is associated with lifestyle behaviours, such as smoking, unhealthy diet, physical inactivity[4] and sedentary behaviour[5]. Physical inactivity is defined as not meeting 150 min weekly practice of moderate physical activity or 75 min of vigorous physical activity. Regardless of the physical activity recommendations, the accumulation of sedentary behaviour, characterized by a series of activities with low energy expenditure (≤ 1.5 metabolic equivalents, *e.g.*, watching television, using the computer, playing video game or riding in a car) throughout the day seems to increase the risk of degenerative chronic diseases and death risk[5]. Over three-quarters of deaths due to cardiovascular diseases could be prevented with adequate changes in lifestyle[4]. Indeed, the adoption of healthy life habits such as increasing physical activity and decreasing sedentary behaviours are able to decrease the risk of type 2 diabetes, stroke, cardiac events and cardiovascular disease[5] improving the quality of life and decreasing risk of death[6]. Several studies have addressed the importance of increasing physical activity levels as a public health intervention[7]. However, even though it is an important factor in primary and secondary prevention[8], the levels of compliance with the physical activity recommendations are still far from desirable[9]. Therefore, enhancing physical activity is still considered a challenge to public health.

The present review draws attention to the importance of physical activity in the primary and secondary prevention of cardiovascular diseases. It also addresses the mechanisms by which physical activity and regular exercise can improve cardiovascular health and reduce the burden of the disease.

PHYSICAL (IN)ACTIVITY AND SEDENTARY BEHAVIOURS

Physical inactivity is the fourth leading risk factor for non-communicable diseases[10]. It is independently responsible for 12.2% of the global burden of acute myocardial infarction[7] as well as 6% of deaths that occur worldwide[9]. Due to its elevated prevalence, physical inactivity is responsible for almost as many deaths as smoking[11,12]. It is estimated to cause 5.3 million deaths worldwide[13] and to increase the risk of diabetes, obesity and several types of cancer[14]. An inactive lifestyle leads to increased blood cholesterol levels and the accumulation of visceral fat; this is accompanied by an innate and adaptive immunological response at cellular and tissue levels leading to a persistent low-grade vascular inflammation, which is a key regulatory mechanism in the pathogenesis of atherosclerosis[15]. The development of atherosclerosis leads to CAD, which becomes evident when it causes thrombosis, angina pectoris and/or myocardial infarction. Inactivity is also associated with low cardiorespiratory fitness, worse mental health and poor quality of life[16].

Time spent in sedentary activities is also associated with an increased risk of cardiovascular diseases and all-cause mortality[17]. Time spent in sedentary activities and mortality show a dose-response relationship, which means that the risk of mortality increases across greater amounts of time spent in sedentary activities, such as sitting or watching TV[18]. In adults who reported daily sitting time in almost none of the time, one fourth of the time, half of the time, three fourths of the time and almost all the time, the adjusted hazard ratios for cardiovascular mortality were 1.00, 1.01, 1.22, 1.47 and 1.54 (P < 0.0001)[18]. It should be noted that the association between sedentary behaviours and mortality is independent of participation in moderate to vigorous leisure-time physical activity[18]. In a recent study, Matthews *et al*[19] showed that excessive amounts of TV viewing (more than 7 h/d *vs* less than 1 h/d) are associated with an increased risk of all-cause and cardiovascular disease mortality, even among adults who reported high levels of moderate to vigorous physical activity (more than 7 h per week). The results of INTERHEART study published recently also demonstrated that subjects who owned both a car and a TV were at higher risk of myocardial infarction (multivariable-adjusted OR = 1.27, 95%CI: 1.05-1.54) compared with those who owned neither[20]. Together, these data suggest that participation in moderate to vigorous physical activity may not be enough to fully attenuate the independent effect of sedentary activities on increased risk for cardiovascular diseases.

PHYSICAL ACTIVITY IN PRIMARY PREVENTION OF CARDIOVASCULAR DISEASES

It has long been demonstrated that physical activity decreases the likelihood of someone developing CAD and to suffer from its consequences[21]. Seminal studies demonstrated that active conductors were protected against CAD compared with inactive bus drivers[22]. These observations were replicated in active postmen compared with inactive telephonists, indicating that people with active occupations were less likely to have adverse events due to CAD[23]. Several studies extended these findings, and showed that physical activity has a graded inverse association with the risk of coronary events[24,25]. Walking is associated with decreased risk of coronary events, with women walking three or more hours per week at a brisk pace having about 35% lower risk of coronary events than those who walk infrequently[25].

Studies conducted in old aged individuals confirmed that physical activity also reduces significantly mortality risk in elderly people without pre-existent cardiovascular disease[26]. Inactive people who become active later in life have also lower risk of cardiovascular events compared with those who remain sedentary[25]. The relation of changes in physical activity and mortality were also seen in men with pre-existent cardiovascular disease[27]. The magnitude of risk reduction is similar as quit smoking[28]. This shows the importance of adopting active lifestyle behaviours, even if initiated during middle or late adulthood during leisure time, as increased leisure time physical activity reduces the risk of cardiovascular events, such as myocardial infarction[20].

In healthy individuals, some of the benefits that physical activity exerts on the prevention of cardiovascular diseases are attributed to positive modifications on traditional risk factors[29]. Maintaining or improving physical activity prevents weight gains and the development of hypertension, hypercholesterolemia, metabolic syndrome, and diabetes, all of which are important cardiovascular risk factors[30,31]. Indeed, physical activity prevents the development of hypertension in normotensive individuals, but it also reduces blood pressure in hypertensive patients[32,33]. In addition, physical activity is associated with better blood cholesterol levels as well as decreased prevalence of obesity and type-II diabetes, all of which contribute to the development of vascular inflammation and atherosclerosis[34]. Many studies have also demonstrated that physical activity reduces blood concentrations of several inflammatory biomarkers such as C-reactive protein, lipoprotein-associated phospholipase A2, cytokines interleukin (IL)-1β, IL-6 and tumor necrosis factor-α, many of which have been recognized as important players in the initiation and development of atherosclerosis[35,36].

On the other hand, it was also shown that physical activity might prevent cardiovascular diseases independently of its potential benefit on other cardiovascular risk factors, including obesity, hypertension and diabetes. This could be related with the increase in physical fitness, which also prevents the burden of the cardiovascular diseases independently of the level of physical activity someone performs[37,38]. Improved physical fitness also attenuates the risk of developing hypertension, increased cholesterol and metabolic syndrome[30], suggesting that both physical activity and physical fitness are independent protective elements of cardiovascular events. A summary of the benefits of physical activity in primary prevention is presented in Table 1.

PHYSICAL ACTIVITY AND CARDIOVASCULAR RISK: INVERSE DOSE-RESPONSE RELATIONSHIP

Whether physical activity is associated with the reduced risk of cardiovascular events is beyond question. The issue that countless researchers have been trying to solve is how much physical activity is needed for reducing the risk of cardiovascular diseases.

Landmark studies showed that death rates declined steadily as energy expended on physical activities increased from less than 500 to 3500 kcal/wk[39]. Death rates were one quarter to one third lower in men expending 2000 or more kcal during exercise per week compared with less active men[39]. The inverse dose-response relationship between physical activity and all-cause mortality was confirmed in recent studies and seems to be stronger in women than in men[40,41]. Individuals who exercise for 90 min/wk have a three year longer life expectancy than inactive people[41]. Every additional 15 min of exercise per day promotes a further 4% risk reduction in all cause-mortality[41]. Moreover, recent meta-analysis of previous studies showed that individuals who engage in the equivalent of 150 min per week of moderate intensity leisure time physical activity have 15% to 20% lower risk of developing CAD than those who undertake no leisure time physical activity[42,43]. Those who perform the equivalent of 300 min/wk of moderate physical activity have even greater risk reduction of coronary artery disease. It is important to note that even persons who did 75 min of moderate intensity physical activity per week had reduced risk of cardiovascular disease, lending credence to the notion that some physical activity is better than none and that additional benefits occur with more physical activity[42].

On the other hand, vigorous physical activity leads to lower incidence of CAD and greater reductions in

Table 1 Summary of the benefits of physical activity in primary prevention

Physical activity in primary prevention	
Prevents	**Improves**
Diseases development associated with cardiovascular disease (hypertension, diabetes and metabolic syndrome)	Physical activity levels and physical fitness (cardiorespiratory fitness and skeletal muscle strength)
Obesity	Prevents weight gains, and improves blood cholesterol profile towards increased HDL blood levels and lower LDL blood levels
Type 2 diabetes	Glycemic control, and improves insulin sensitivity in type 2 diabetics
Hypertension	Prevents the development of hypertension in normotensive individuals, and reduces blood pressure in hypertensive patients
Vascular inflammation and atherosclerosis	Reduces blood concentrations of several inflammatory biomarkers such as C-reactive protein, lipoprotein-associated phospholipase A2, cytokines IL-1β, IL-6 and TNF-α

TNF: Tumor necrosis factor; HDL: High density cholesterol; LDL: Low density cholesterol; IL: Interleukin.

all-cause mortality[44,45]. However, not all studies have controlled for exercise volume, advising caution in the interpretation of these results. These results are consistent with the recent recommendations suggesting that healthy adults should perform at least 150 min of moderate intensity aerobic exercise (40%-60% of heart rate reserve) or 75 min of vigorous intensity physical activity (60%-85% of heart rate reserve) per week or through the equivalent combination of moderate and vigorous-intensity physical activities[46]. Very recently, pooled data from population-based prospective cohorts in the United States and Europe, including a total of 661137 men and women, with a median follow-up of 14.2 years, showed that risk of mortality was 20% lower among individuals performing less than the recommended minimum of leisure time physical activity [HR = 0.80 (95%CI: 0.78-0.82)], with this inverse association growing stronger among those reporting 1 to 2 times [HR = 0.69 (95%CI: 0.67-0.70)] or 2 to 3 times the recommended minimum [HR = 0.63 (95%CI: 0.62-0.65)] leisure time physical activity[47]. Interestingly the association appears to reach a threshold among persons performing higher levels of physical activity, suggesting that inactive individuals may benefit from modest amounts of physical activity in terms of reducing mortality while high levels of physical activity does not confer increased risk of mortality[47]. Additionally, maximum longevity benefit seems to be associated with meeting the recommended guidelines for moderate to vigorous physical activity[47]. Health benefits are also achieved when sedentary behaviours are replaced by light intensity physical activity (< 40% of heart rate reserve) and moderate to vigorous activities are held constant[48]. Reducing sedentary activities should be pursued by everyone independent of the amount and intensity of physical activity one achieves per week, as sitting time or time spent watching television is independently associated with greater incidence of cardiovascular risk factors, cardiovascular disease and cardiac mortality[18,49].

PHYSICAL ACTIVITY IN SECONDARY PREVENTION OF CARDIOVASCULAR DISEASES

Physical activity also plays an important role in secondary prevention of cardiovascular diseases by reducing the impact of the disease, slowing its progress and preventing recurrence. Nonetheless, it is difficult to ascertain the role of leisure time physical activity alone in secondary prevention, as most studies have not discerned the effects of structured exercise training alone or incorporated in comprehensive cardiac rehabilitation programs from those induced by leisure time physical activity alone. In patients following myocardial infarction, participation in an 8-wk exercise-based cardiac rehabilitation programme was found to improve leisure-time physical activity levels consistent with health-related benefits[50]. Interestingly, at baseline, only half of the subjects were compliant with physical activity recommendations (52%), but at the end of the intervention, 76% of the exercise group and 44% of controls complied with physical activity recommendations[50]. Likewise, a home-based cardiac rehabilitation program, composed by education and counselling intervention for 12 wk, regarding physical activity and cardiovascular risk factor management, showed an increase in physical activity index and time spent in moderate to vigorous physical activity during the intervention period with no changes in the control group[51].

Despite the well-known benefits of physical activity and exercise training, most of eligible cardiovascular patients do not benefit from cardiac rehabilitation programs[52], and these patients are more likely to taking less exercise[53]. Exercise levels may even decrease after the diagnosis of heart disease. The least active subjects are more likely to be older, male, obese and present symptoms during common activities such as short distance walking[53].

Participation in cardiac rehabilitation programs has been associated with decreased mortality and recurrent myocardial infarction, with compliant patients showing greater risk reduction when compared to patients with less attendance to exercise training sessions[54,55]. A recent meta-analysis including patients who have had myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, angina pectoris or CAD defined by angiography confirmed that exercise-based cardiac rehabilitation programs are effective in reducing total and cardiovascular mortality (in medium and long term) and hospital admissions (in shorter term) but not the risk of myocardial infarction and revascularization[56]. Even though smoking cessation and nutritional counselling can also contribute for these positive outcomes, exercise training has an independent effect in the prevention of cardiovascular death[57]. Exercise-based cardiac rehabilitation programs promote an increase in cardiorespiratory fitness, a strong predictor of all-cause mortality, but also increase leisure time physical activity levels[51]. Hambrecht *et al*[58] demonstrated that estimated energy expenditure during leisure time physical activity is correlated with changes in coronary stenosis diameter independent of attendance in formal exercise interventions. Energy expenditure was lower in patients with progression of coronary atherosclerosis, higher in patients with no change, and highest in patients with regression of coronary stenosis diameter. High workloads were needed (about 1500 kcal/wk) to halt progression of coronary atherosclerosis, and regression of atherosclerosis was observed only in patients expending an average of 2200 kcal/wk in leisure time physical activity, corresponding to approximately 4 to 6 h of moderate intensity physical activity per week. A summary of the benefits of physical activity in secondary prevention is presented in Table 2.

Table 2 Summary of the cardiovascular protection mechanisms induced by physical activity in secondary prevention

Physical activity in secondary prevention	
Decreases	**Increases**
Resting heart rate	Heart rate reserve
Resting systolic blood pressure	Diastolic function
Myocardial oxygen demand	Coronary circulation
Risk of myocardial ischemia	Myocardial perfusion
Sympathetic tone	Parasympathetic activity
Arterial Stiffness	Endothelial function
Low-grade vascular inflammation (levels of pro-inflammatory cytokines)	Nitric oxide bioavailability and circulating levels of endothelial progenitor cells
Expression of reactive oxygen species	Expression and activity of anti-oxidant enzymes
Resting levels of plasminogen activator inhibitor type 1	Resting levels of tissue plasminogen activator activity
Platelet adhesion and aggregation	

CARDIOVASCULAR PROTECTION MECHANISMS INDUCED BY PHYSICAL ACTIVITY IN SECONDARY PREVENTION

It is well established that physical activity lowers resting heart rate and systolic blood pressure and increases heart rate reserve in patients with heart disease[59,60], thereby decreasing myocardial oxygen demands and preventing myocardial ischemia for a given absolute exercise intensity[61]. This may stem from a restored function of the autonomic nervous system towards lower sympathetic tone and enhanced parasympathetic activity[60,62]. In addition, aerobic physical activity improves myocardial perfusion in CAD patients, as a result of improved endothelial function, enhanced coronary circulation and vasomotor responses to vasoactive substances[63].

Aerobic physical activity seems to improve endothelial function in response to increases in blood flow-mediated shear stress, stimulating the endothelial production of nitric oxide and preventing its degradation by reactive oxygen species[64]. In addition, physical activity mitigates vascular inflammation while it improves anti-oxidant defences, also contributing for improving endothelial dysfunction[64-66]. Physical activity also promotes the mobilization of endothelial progenitor cells into the circulation to maintain endothelial integrity and stimulate vascular regeneration and endothelial repair[67,68].

Arterial stiffness has also been shown to decline in active individuals[69], as well as in CAD patients after cardiac rehabilitation[70,71], changes that may reduce aortic systolic blood pressure and cardiac afterload, increasing coronary perfusion and preventing myocardial ischemia as a result. A recent randomized controlled trial did not find significant changes between groups in arterial stiffness after an 8-wk exercise training program in post-myocardial infarction patients under optimized medication; however, when excluding those patients who did not attend, at least 80% of the exercise sessions, the authors found a significant reduction in arterial stiffness when compared to the control group[72].

In addition, a sedentary lifestyle during healthy aging is associated with decreased left ventricular compliance, leading to diminished diastolic performance, while prolonged, sustained endurance training seems to preserve ventricular compliance with aging[73] and to enhance diastolic function in heart failure patients[74,75]. Moderate to vigorous physical activity may also offer protection against cardiac events by inducing short-term transient ischemia, conferring a window of protection against an ischemic insult of longer duration, a phenomenon known as cardiac preconditioning[76,77]. It has been demonstrated in patients with old myocardial pectoris or angina pectoris that a single bout of physical exercise is capable of reducing exercise-induced ST-segment depression[78]. Prevention of coronary events may also stem from antithrombotic effects, even though evidence supporting an association between regular physical activity and decreased risk of thrombus formation and plaque rupture is scarce[79].

Acute strenuous physical activity seems to be associated to increased platelet adhesiveness and aggregation, increased thrombin formation and increased activity of several coagulation factors[80,81]. Nonetheless, regular moderate physical activity has been shown to blunt platelet adhesion and aggregation in healthy sedentary individuals[82] and heart failure patients[83]. Blood coagulation prospect after plaque rupture appears to diminish with regular physical activity, with studies finding lower plasma levels of several haemostatic factors in active individuals and women with CAD[84,85]. Inverse dose-response association between physical activity and circulating levels of fibrinogen has been reported[86] and regular aerobic exercise seems to increase resting tissue plasminogen activator activity and to reduce plasminogen activator inhibitor type 1 in older adults[87,88].

SUMMARY

Physical inactivity is one of the four leading risk factors of non-communicable diseases, in particular those related with cardiovascular diseases such as acute coronary syndromes, stroke and heart failure. Despite this evident association, prevalence of physical inactivity is still elevated worldwide, being directly responsible for almost one tenth of premature death from non-communicable diseases. Even though physical activity has been shown to play an important role in primary and secondary prevention of cardiovascular diseases and major cardiovascular events, regular participation in physical activity is still below the necessary threshold to improve cardiorespiratory fitness and confer cardiac protection in many subjects. Reducing sedentary behaviours and performing less than the recommended minimum leisure time physical activity may be sufficient to reduce mortality, but meeting the recommended guidelines of moderate- or vigorous-intensity physical activities and reducing sedentary behaviours is associated with higher health benefits. Therefore, health professionals and policy makers in public health should align strategies to increase participation in physical activity, especially among those who show less interest or availability to engage in regular physical activity.

FUTURE PERSPECTIVES

The above-mentioned results are promising and provide good perspectives for the future.

Over the last decades the standard of living and physical activity profile performed throughout the day has been changing in societies around the world in parallel to the high death rates caused by CAD. Recent studies have addressed the time spent in sedentary behaviours as a risk factor for CAD, regardless of the amount and intensity of physical activity done. Taking these data into consideration, future studies should addresses both the causes and effects of both sedentary behaviour and physical inactivity in bodily adaptations and its relations with the development of cardiovascular disease.

It is also suggested that future studies evaluate the relationship between different covariates that may influence the effects of physical activity, such as age, sex, ethnicity, educational and/or socioeconomic status, and occupational and leisure-time contexts, in order to identify more assertively public health intervention strategies so that physical activity and exercise programs can be optimized for reducing the number of deaths caused by cardiovascular complications.

Although substantial evidence exists demonstrating the benefits of exercise training, referral to and participation in cardiac rehabilitation programs is still less than half among all eligible patients with cardiovascular diseases. Thus, more research is needed to identify common barriers to participation in physical activity programs, not only in the general population but also in special populations and minorities, and to understand how such barriers can be broken down to increase participation in physical activity.

Thus, we believe that such strategies could have important beneficial effects on the reduction of deaths caused by cardiovascular disease from the primary and secondary prevention.

ACKNOWLEDGMENTS

CIDESD is a research unit supported by the Portuguese Foundation for Science and Technology, (UID/DTP/04045/2013) and by the European Regional Development Fund, through COMPETE 2020 (POCI-01-0145-FEDER-006969). This research is part of NanoSTIMA: Macro-to-Nano Human Sensing: Towards Integrated Multimodal Health Monitoring and Analytics, funded by the European Regional Development Fund, through NORTE 2020 (NORTE-01-0145-FEDER-000016). The European Regional Development Fund through the Operational Competitiveness Program, and the Foundation for Science and Technology (FCT) of Portugal support the research unit CIAFEL within the projects FCOMP-01-0124-FEDER-020180 (References FCT: PTDC/DES/122763/2010) and UID/DTP/00617/2013, respectively. iBiMED is a research unit supported by the Portuguese Foundation for Science and Technology (REF: UID/BIM/04501/2013) and FEDER/Compete2020 funds.

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P- Reviewer: Amiya E, Nunez-Gil IJ **S- Editor**: Gong XM
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World Journal of Cardiology

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DOI: 10.4330/wjc.v8.i10.584

World J Cardiol 2016 October 26; 8(10): 584-589
ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Basic Study

Impaired norepinephrine regulation of monocyte inflammatory cytokine balance in heart failure

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Author contributions: Ng TMH was involved in the design, conduct of the study, statistical analysis, and authorship of the manuscript; Toews ML was involved in the design and assays related to the study.

Supported by the American College of Clinical Pharmacy Research Institute.

Institutional review board statement: Study was approved by the University of Nebraska Medical Center Institutional Review Board.

Informed consent statement: The protocol was approved by the Institutional Review Board of the university. All human subjects gave signed informed consent for their participation.

Conflict-of-interest statement: The authors report no conflicts of interest related to the study.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

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Received: March 10, 2016
Peer-review started: March 15, 2016
First decision: April 20, 2016
Revised: July 27, 2016
Accepted: August 17, 2016
Article in press: August 18, 2016
Published online: October 26, 2016

Abstract

AIM

To evaluate the effect of norepinephrine on inflammatory cytokine expression in *ex vivo* human monocytes and monocytic THP-1 cells.

METHODS

For human monocyte studies, cells were isolated from 12 chronic heart failure (HF) (66 ± 12 years, New York Heart Association functional class III-IV, left ventricular ejection fraction 22% ± 9%) and 14 healthy subjects (66 ± 12 years). Monocytes (1 × 10^6/mL) were incubated with lipopolysaccharide (LPS) 100 ng/mL, LPS + norepinephrine (NE) 10^{-6} mol/L or neither (control) for 4 h. Tumor necrosis factor-alpha (TNFα) and interleukin-10 (IL-10) production were determined by ELISA. Relative contribution of α- and β-adrenergic receptor subtypes on immunomodulatory activity of NE was assessed in LPS-stimulated THP-1 cells incubated with NE, the α-selective agonist phenylephrine (PE), and the β-selective agonist isoproterenol (IPN). NE-pretreated THP-1 cells were also co-incubated with the β-selective antagonist propranolol (PROP), α2-selective antagonist yohimbine (YOH) or the α1-selective antagonist prazosin (PRAZ).

RESULTS

Basal TNFα concentrations were higher in HF *vs* healthy subjects (6.3 ± 3.3 pg/mL *vs* 2.5 ± 2.6 pg/mL, P = 0.004). Norepinephrine's effect on TNFα production was reduced in HF (-41% ± 17% HF *vs* -57% ± 9% healthy, P = 0.01), and proportionately with NYHA FC. Increases in IL-10 production by NE was also attenuated in HF (16% ± 18% HF *vs* 38% ± 23% healthy, P = 0.012). In THP-1 cells, NE and IPN, but not PE, induced a dose-dependent suppression of TNFα. Co-incubation with NE and antagonists revealed a dose-dependent inhibition of the NE suppression of TNFα by PROP, but not by YOH or PRAZ. Dose-dependent increases in IL-10 production were seen with NE and IPN, but not with PE. This effect was also antagonized by PROP but not by YOH or PRAZ. Pretreatment of cells with IPN attenuated the effects of NE and IPN, but did not induce a response to PE.

CONCLUSION

NE regulation of monocyte inflammatory cytokine production may be reduced in moderate-severe HF, and may be mediated through β-adrenergic receptors.

Key words: Monocytes; Cytokines; Heart failure; Inflammation

Core tip: In evaluating the relationship between sympathetic activation and inflammatory cytokine production in heart failure, we demonstrated that norepinephrine (NE) has reduced ability to suppress the production of the proinflammatory cytokine tumor necrosis factor-alpha, and increase anti-inflammatory interleukin-10, in human isolated monocytes from heart failure compared to healthy subjects. It appears to be mediated through beta-adrenergic, and not alpha-adrenergic, receptors based on monocytic THP-1 cells dose-response experiments. This suggests that the diminished immunomodulatory activity of NE in heart failure is primarily due to altered beta-adrenergic receptor function, and may represent an immunologic mechanism for the positive effects of beta-adrenergic blocking agents.

Ng TMH, Toews ML. Impaired norepinephrine regulation of monocyte inflammatory cytokine balance in heart failure. *World J Cardiol* 2016; 8(10): 584-589 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i10/584.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i10.584

INTRODUCTION

The importance of inflammatory cytokines to the pathophysiology of heart failure (HF) has been recognized for many years[1]. Much of the focus has been on proinflammatory tumor necrosis factor-alpha (TNFα) which has been shown to be cardiodepressant, contributes to exercise intolerance, and modulates apoptosis, oxidative stress and endothelial dysfunction[2,3]. Interleukin-10 (IL-10) antagonizes the inflammatory effects of TNFα. Both TNFα and IL-10 plasma levels are elevated in HF patients, although the increase in IL-10 is proportionately less, supporting the notion of a proinflammatory state[4].

Pro- and anti-inflammatory cytokine production is regulated by the adrenergic nervous system. Previous studies have demonstrated that β_2-, but not β_1-, receptor agonists attenuate TNFα expression, while increasing anti-inflammatory IL-10 production[5,6]. Conversely, $\alpha_{1,2}$-adrenergic stimulation results in increased expression of TNFα and reduction in IL-10[7]. Under normal physiologic conditions, norepinephrine, an α- and β-agonist, reduces TNFα and enhances IL-10 expression in monocytes exposed to lipopolysaccharide (LPS) and other stimuli[8]. However, in HF a paradox exists as both catecholamines and TNFα are elevated, which suggests that this negative feedback mechanism may be impaired. The mechanism for the diminished immunomodulatory response to norepinephrine in HF is also unknown but could occur secondary to the altered adrenergic expression and function known to exist in the failing heart.

The study purpose was to evaluate whether attenuation of TNFα production and augmentation of IL-10 production by the adrenergic agonist norepinephrine is altered in chronic HF compared to healthy, age-matched controls utilizing the model of LPS-stimulated monocytes. In addition, preliminary experiments were undertaken to determine the relative contribution of α- and β-adrenergic receptor subtypes on the immunomodulatory activity of norepinephrine in monocytic THP-1 cells.

MATERIALS AND METHODS

Isolated human monocytes

HF subjects were recruited from the cardiology clinics and the University Hospital at the University of Nebraska Medical Center. Subjects, male or female, were eligible for inclusion if they had: Clinical HF (LVEF < 40% on 2D-ECHO or MUGA within last 3 mo), New York Heart Association Functional Class (NYHA FC) III-IV HF, and were over 30 years of age. Exclusion criteria included: Primary restrictive or valvular HF, acute viral illness or bacterial infection, history of autoimmune disease, concurrent therapy with systemic norepinephrine, known anemia (Hgb < 10 mg/dL) or other contraindication to giving blood. Healthy subjects over the age of 30 were recruited from the University of Nebraska Medical Center through a posting on the university Intranet. All human subjects gave informed consent for their participation. The protocol was approved by the Institutional Review Board of the university.

Monocyte isolation was performed following a standard Nycodenz protocol[9], from 12 HF [age 66 ± 12 years old, New York Heart Association Functional Class (NYHA FC) 6 III, 6 IV, mean left ventricular ejection fraction 20% ± 10%] and 14 healthy subjects (age 66 ± 12 years). Aliquoted (1 x 10^6/mL) monocytes were

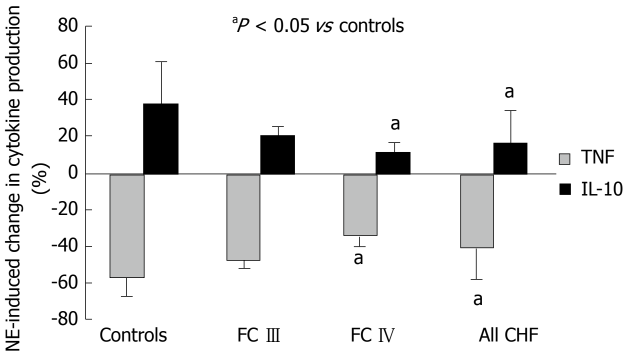

Figure 1 Comparative change in lipopolysaccharide-induced tumor necrosis factor-alpha and interleukin-10 production in monocytes induced by norepinephrine between heart failure patients and normal controls. Results expressed as mean ± SD. FC: Functional classification.

incubated with LPS 100 ng/mL, LPS + norepinephrine 10^{-6} mol/L or neither (negative control) for 4 h (all reagents from Sigma Chemical Co., Westbury, NY). Previous work demonstrated maximal stimulation of cytokines using the specified reagent concentrations and incubation time. TNFα and IL-10 production were determined by assaying the supernatant using commercially available enzyme-linked immunoassay (ELISA) kits (R and D Systems, Minneapolis, MN).

THP-1 cells

THP-1 cells were cultured and assayed in a supplemented RPMI media (ATCC, Manassas, VA). Cells were aliquoted into 1 × 10^6 cells/mL samples for experiments. Dose-response curves were determined for TNFα and IL-10 production in LPS-stimulated (100 ng/mL) THP-1 cell samples incubated with norepinephrine (10^{-5} to 10^{-10} mol/L), the α-selective agonist phenylephrine (PE) (10^{-6} to 10^{-10} mol/L) and the β-selective agonist isoproterenol (IPN) (10^{-5} to 10^{-10} mol/L). LPS-stimulated THP-1 cells were also co-incubated with a fixed concentration of norepinephrine 10^{-6} mol/L, which provided maximal effect in agonist experiments, and the β-selective antagonist propranolol (PROP) (10^{-5} to 10^{-10} mol/L), α2-selective antagonist yohimbine (YOH) (10^{-6} to 10^{-10} mol/L) or the α1-selective antagonist prazosin (PRAZ) (10^{-6} to 10^{-10} mol/L), for generation of dose-response curves. TNFα and IL-10 production was assessed as described above. Samples were assayed in duplicate.

Statistical analysis

To control for inherent inter-subject differences in constitutive production of cytokines, changes in TNFα and IL-10 concentrations are expressed as percent reduction by norepinephrine + LPS compared to LPS only for each sample. Comparison of percent reduction in TNFα and IL-10 concentrations from isolated monocytes of controls and HF subjects was performed by an independent two sample *t* test. Significance was set at $P < 0.05$. Results are reported as mean ± SD. Comparative effects on cytokine production in THP-1 cells between the different α- and β-adrenergic reagents

Table 1 Patient characteristics

%	Heart failure (*n* = 12)	Healthy subjects (*n* = 14)	*P* value
Age (yr)	66 ± 12	66 ± 12	0.994
Male	67	36	0.238
Caucasian ethnicity	92	100	0.462
LVEF	22 ± 9		
Diabetes	33	0	0.033
CAD	50	0	0.004
Hypertension	25	29	1.000
Medications			
Beta-blocker	50	0	
ACE inhibitor or ARB	75	7	
Loop diuretic	100	0	
ARA	42	0	
Hydralazine/isosorbide dinitrate	8	0	
Amiodarone	50	0	
Digoxin	50	0	

ACE: Angiotensin converting enzyme inhibitor; ARA: Aldosterone receptor blocker; ARB: Angiotensin receptor blocker; CAD: Coronary artery disease; LVEF: Left ventricular ejection fraction.

was assessed *via* visual inspection of the dose-response curves as this was a preliminary study. The statistical methods of this study were reviewed by Mimi Lou, MS (biostatistician) from the University of Southern California School of Pharmacy.

RESULTS

Isolated human monocytes

Study subject characteristics are described in Table 1. Basal TNFα concentrations (supernatant) were higher in HF than healthy subjects (6.3 ± 3.3 pg/mL *vs* 2.5 ± 2.6 pg/mL, *P* = 0.004). Norepinephrine reduction of TNFα production was significantly reduced in monocytes from HF subjects (-41% ± 17% HF *vs* -57% ± 9% healthy, *P* = 0.01). Norepinephrine-induced increases in monocyte IL-10 production was also reduced in HF (16% ± 18% HF *vs* 38% ± 23% healthy, *P* = 0.012). The diminished response to norepinephrine appeared related to severity of HF, with a greater diminution for both TNFα and IL-10 in NYHA FC IV *vs* NYHA FC III and controls (Figure 1). A signal for reduced IL-10 response in patients with left ventricular ejection fractions ≤ 20% when compared to those with left ventricular ejection fractions > 20% (7% ± 12 *vs* 25% ± 20%, *P* = 0.07) was also present. There were no differences in cytokine response based on the presence or absence of beta-blocker (BB) therapy (TNFα: -37% ± 17% no BB *vs* -46% ± 17% BB, *P* = 0.9; IL-10: 11% ± 13% no BB *vs* 20% ± 22% BB, *P* = 0.3), or HF etiology (TNFα: -41% ± 17% ischemic *vs* -42% ± 18% non-ischemic, *P* = 0.7; IL-10: 20% ± 19% ischemic *vs* 8% ± 15% non-ischemic, *P* = 0.5).

THP-1 cells

Norepinephrine and IPN, but not PE, induced a concentration-dependent suppression of TNFα production

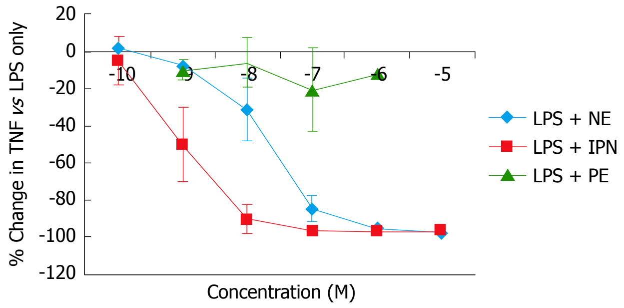

Figure 2 Concentration-dependent changes in lipopolysaccharide-induced tumor necrosis factor-alpha production in monocytic THP-1 cells induced by the α-adrenergic agonist phenylephrine and the β-adrenergic agonist isoproterenol. Results expressed as mean ± SD. LPS: Lipopolysaccharide; NE: Norepinephrine; IPN: Isoproterenol; PE: Phenylephrine.

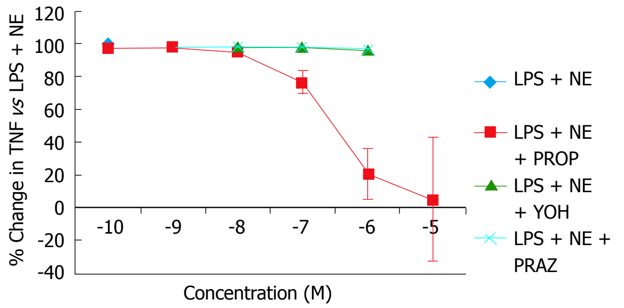

Figure 3 Concentration-dependent changes in norepinephrine attenuation of lipopolysaccharide-induced tumor necrosis factor-alpha production in monocytic THP-1 cells blocked by the α1-adrenergic antagonist prazosin, the α2-adrenergic antagonist yohimbine, and the β-adrenergic antagonist propranolol. Results expressed as mean ± SD. LPS: Lipopolysaccharide; NE: Norepinephrine; PE: Phenylephrine; PROP: Propranolol; YOH: Yohimbine; PRAZ: Prazosin.

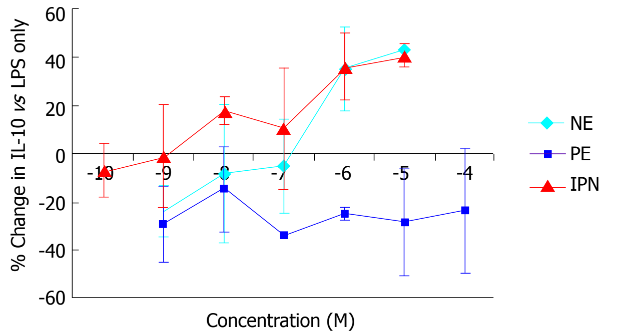

Figure 4 Concentration-dependent changes in interleukin-10 production in THP-1 cells induced by the α-adrenergic agonist phenylephrine and the β-adrenergic agonist isoproterenol. Results expressed as mean ± SD. NE: Norepinephrine; IPN: Isoproterenol; PE: Phenylephrine; LPS: Lipopolysaccharide; IL: Interleukin.

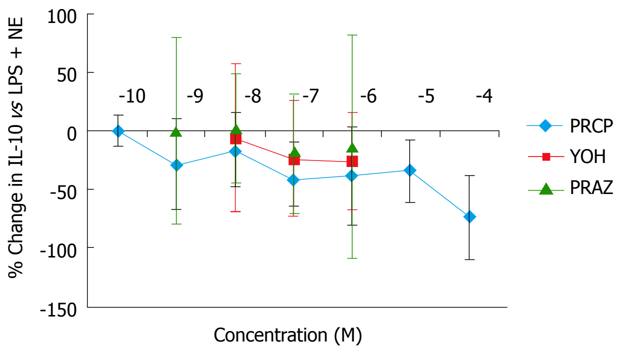

Figure 5 Concentration-dependent changes in norepinephrine attenuation of interleukin-10 production in THP-1 cells blocked by the α1-adrenergic antagonist prazosin, the α2-adrenergic antagonist yohimbine, and the β-adrenergic antagonist propranolol. Results expressed as mean ± SD. LPS: Lipopolysaccharide; NE: Norepinephrine; PE: Phenylephrine; PROP: Propranolol; YOH: Yohimbine; PRAZ: Prazosin.

in cultured monocytic THP-1 cells. Equivalent maximal suppression was achieved with norepinephrine 10^{-6} mol/L or IPN 10^{-7} mol/L (Figure 2). Co-incubation of THP-1 cells with LPS, norepinephrine and selective adrenergic receptor antagonists revealed a concentration-dependent inhibition of the norepinephrine suppression of TNFα by PROP, but not by YOH or PRAZ. Maximal blockade of norepinephrine's effects was obtained at PROP 10^{-5} mol/L (Figure 3). Concentration-dependent increases in IL-10 production were seen with norepinephrine and IPN, but not with PE (Figure 4). This effect was also antagonized by PROP but not by YOH or PRAZ (Figure 5). Pretreatment of cells with IPN (10^{-7} mol/L) for 4 h attenuated the effects of norepinephrine and IPN, but pretreatment did not induce a response to PE (data not shown).

DISCUSSION

Our preliminary findings suggest norepinephrine's ability to regulate monocyte inflammatory cytokine production may be reduced in moderate to severe HF. The ability of norepinephrine to exert an overall anti-inflammatory effect on the balance of production of TNFα and IL-10 appears to be reduced in proportion to disease severity, as indicated by the a greater diminution of the induced cytokine response in monocytes isolated from NYHA functional class Ⅳ as compared to functional class Ⅲ patients and controls. This is the first report demonstrating monocyte TNFα/IL-10 responsiveness to norepinephrine is diminished in HF and provides a novel mechanism to explain increased production of TNFα in HF. Our results are consistent with a study demonstrating a reduced inhibitory effect of norepinephrine on TNFα production assessed in whole blood of HF patients[10]. Our results also agree with other studies demonstrating basal monocytic inflammatory cytokine production is upregulated in chronic HF[11,12].

In addition, based on our experiments in monocytic THP-1 cells, norepinephrine's immunomodulatory effect in monocytes is likely secondary to activation of β-adrenergic receptors, with no or little involvement of α-adrenergic receptors. This was evidenced by the concentration-dependent reduction of TNFα and augmentation of IL-10 production by norepinephrine and isoproterenol, but not by phenylephrine. The effect of norepinephrine could also be antagonized by β-receptor blockade with propranolol, whereas α1 and α2-blocking agents had no effect. This is consistent with other investigations and provides a plausible mechanism for the diminished cytokine response to norepinephrine observed in HF[13-16]. Altered β-adrenergic receptor function and expression have been well characterized in the failing heart[17,18]. Beta1-adrenergic receptor density and function is reduced in the failing heart, while beta-2-adrenergic receptor expression remains essentially unchanged[19]. This shift in importance towards the beta-2-adrenergic receptor would suggest immunomodulatory response to catecholamines would be preserved, however, other pathophysiologic alterations may still occur that change or limit their functionality[20,21]. In addition, norepinephrine is known to have low affinity for beta2-adrenergic receptors, but showed similar maximal effects comparable to isoproterenol[22,23]. Therefore, whether the observed immunomodulatory response to norepinephrine is mediated solely through beta2-adrenergic receptors requires confirmation.

The study has important limitations. The human monocyte experiment sample size is small. Unfortunately we did not have an adequate number of human monocytes to evaluate adrenoreceptor expression between HF and healthy subjects which would strengthen these preliminary findings as THP-1 are a monocytic cell-line but may not be identical to human monocytes. We also did not examine the isolated effects of the receptor antagonists propranolol, yohimbine and prazosin as we are not aware of literature suggesting a direct effect on inflammatory cytokine production, only modulation in a proinflammatory model[6,7,13,14,24-27]. As such, the results of this study are preliminary and should be interpreted as hypothesis generating. Further studies are required to determine whether monocyte production of other cytokines exhibit a similar reduction in response to catecholamine stimulation in HF, to fully characterize the mechanism for the observed impaired catecholamine-cytokine response, and to devise pharmacologic strategies to normalize cytokine responsiveness to the adrenergic nervous system.

ACKNOWLEDGMENTS

The authors would like to thank Amy Vrana for her help performing assays for this study. The authors would also like to thank Tom Sears, MD for his assistance with identifying heart failure subjects for the study.

COMMENTS

Background

Inflammation has been recognized as a major contributing factor to the pathophysiology of heart failure (HF) with reduced ejection fraction (HFrEF) for many years. However, attempts to improve the prognosis of HFrEF patients by targeting proinflammatory cytokines have failed largely in part to an incomplete understanding of the mechanisms which contribute to the initiation and perpetuation of their expression. Pro- and anti-inflammatory cytokine production is regulated by the adrenergic nervous system. Under normal physiologic conditions, norepinephrine, an α- and β-agonist, reduces tumor necrosis factor-alpha (TNFα) and enhances interleukin-10 expression in monocytes exposed to lipopolysaccharide and other stimuli. However, in HFrEF a paradox exists as both catecholamines and TNFα are elevated, which suggests that this negative feedback mechanism may be impaired.

Research frontiers

HF is recognized as a proinflammatory syndrome, and that inflammatory pathways likely contribute to the decline in cardiac function. However, the mechanisms for initiation or persistence of the proinflammatory balance are poorly described and remain an area of active investigation. Clinical trials of agents targeting proinflammatory cytokines have failed to improve long term prognosis of HF patients. A major explanation for the failures is an incomplete understanding of mechanisms underlying the proinflammatory state.

Innovations and breakthroughs

Although it has been described that catecholamines reduce proinflammatory cytokine production, this is the first study to demonstrate that attenuation of monocyte inflammatory cytokine production by norepinephrine is reduced in cells isolated from HF patients compared to healthy individuals.

Applications

The findings are mainly descriptive but may represent a novel pathway for the proinflammatory state in patients with HF. If alterations in β-adrenergic receptor function is a mechanism for the diminished counter-regulatory response to norepinephrine in HF, some of the benefit of beta-adrenergic receptor blockers in HF may be due to immunomodulatory or anti-inflammatory effects. These preliminary findings need confirmation in future studies.

Peer-review

The manuscript is interesting because it adds new information concerning mechanisms underlying this proinflammatory state.

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P- Reviewer: Amiya E, Gong KZ, Grignola J, Iacoviello M, Lymperopoulos A **S- Editor**: Kong JX **L- Editor**: A **E- Editor**: Wu HL

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DOI: 10.4330/wjc.v8.i10.590

World J Cardiol 2016 October 26; 8(10): 590-595
ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Retrospective Study

Left ventricular false tendons and electrocardiogram repolarization abnormalities in healthy young subjects

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Author contributions: All authors contributed equally to this work; Lazarevic Z collected and analyzed the data and drafted the manuscript; Lazarevic Z and Borrione P designed and supervised the study; Ciminelli E, Quaranta F, Sperandii F, Guerra E, Pigozzi F and Borrione P revised the manuscript for important intellectual content; all the authors have read and approved the final version to be published.

Institutional review board statement: This study retrospectively and anonymously analyzed clinical data routinely collected during the pre-participation screening of competitive athletes. For this reason, ethics committee approval was not required.

Informed consent statement: Subjects were not required to give informed consent for the study since the analysis used anonymous clinical data.

Conflict-of-interest statement: There are no financial or other relationships that might lead to a conflict of interest in this study.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

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Received: March 8, 2016
Peer-review started: March 9, 2016
First decision: May 17, 2016
Revised: July 15, 2016
Accepted: August 6, 2016
Article in press: August 8, 2016
Published online: October 26, 2016

Abstract

AIM

To describe echocardiographically left ventricular false tendon characteristics and the correlation with ventricular repolarization abnormalities in young athletes.

METHODS

Three hundred and sixteen healthy young athletes from different sport disciplines were evaluated from 2009 to 2011 during routine screening for agonistic sports eligibility. All subjects, as part of standard pre-participation screening medical evaluation, underwent a basal and post step test 12-lead electrocardiogram (ECG). The athletes with abnormal T-wave flattening and/or inversion were considered for an echocardiogram evaluation and an incremental maximal exercise test on a cycle ergometer. Arterial blood pressure and heart rate, during and after exercise, were also measured.

RESULTS

Twenty-one of the 316 subjects (6.9%) showed false tendons in the left ventricle. The majority of false tendons (52.38%) were localized between the middle segments of the inferior septum and the lateral wall, 19.06% between the distal segments of the septum and the lateral wall, in 5 subjects between the middle segments of the anterior and inferior walls, and in one subject between the middle segments of the anterior septum and the posterior wall. ECG abnormalities, represented by alterations of ventricular repolarization, were found in 11 subjects (52.38%), 90% of these anomalies were T wave abnormalities from V1 to V3. These anomalies disappeared with an increasing heart rate following the three minute step test as well as during the execution of the maximal exercise.

CONCLUSION

Left ventricular false tendons are frequently localized between the middle segments of the inferior septum and the lateral wall and are statistically associated with ventricular repolarization abnormalities.

Key words: Repolarization anomalies; T wave inversion; Young athletes; False chordae tendineae; Echocardiography

Core tip: Ventricular repolarization abnormalities of subjects with false tendons were most frequently inverted T waves from V1 to V3. In this study, statistically significant associations between the presence of false tendons in the left ventricle and ventricular repolarization abnormalities in young healthy athletes were found. Furthermore, this study provides useful information for sports physicians when basic electrocardiogram abnormalities of ventricular repolarization are considered.

Lazarevic Z, Ciminelli E, Quaranta F, Sperandii F, Guerra E, Pigozzi F, Borrione P. Left ventricular false tendons and electrocardiogram repolarization abnormalities in healthy young subjects. *World J Cardiol* 2016; 8(10): 590-595 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i10/590.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i10.590

INTRODUCTION

"False tendons" are fibrous, fibrous-muscle or muscle structures, variable in length and thickness, found in the left ventricular cavity, generally located between the free wall of the left ventricle or a papillary muscle and the interventricular septum, without connection to the mitral valves[1-3]. Turner first described the false tendons in the left ventricle (LVFT) in 1893 but the functional significance of these structures is still unclear[4].

The left ventricular false tendons are easily identifiable with bi-dimensional echocardiography. They are usually found in about 50% of autoptical examinations[5-8], most frequently in males[4,9]. The prevalence of false tendons in the left ventricle appears to be higher in young athletes than in the general population (6.9% *vs* 0.5% to 4.6%)[7]. This difference can be attributed to an increased use of echocardiography in young athletes. However, a young athlete often has excellent acoustic windows, physiological bradycardia and enlargement of the ventricular cavity, which permit better identification of all structures inside the ventricular cavity and in particular, the trabeculae or fibrous-muscle structures, stretched between the walls of the ventricle[10].

The primary characteristic of the false tendons to be emphasized is their tension or laxity inside the left ventricular cavity during the cardiac cycle. More frequently, false tendons are stretched in diastole and are flaccid in systole (from 71.4% to 86% of cases); in some cases they are in tension for the entire cardiac cycle (10.6%-15.4%), while in rare cases they remain flaccid for the entire cycle (1.2%-2.8%).

This type of information is very useful since the stretching of these ventricular structures can play an important role in the genesis of electrocardiographic abnormalities or real arrhythmias. This mechanical phenomenon is also the basis of the genesis of a murmur that can be appreciated on auscultation in some subjects with false tendons[1,11]. Generally, LVFTs have been considered a normal variation but in some cases, they may be related to cardiac pre-excitation, ventricular arrhythmias, dilation of the left ventricle, congenital and/or acquired heart diseases and some repolarization abnormalities on resting electrocardiograms (ECGs), including negative or biphasic T waves in precordial leads as well as early repolarization[12].

A literature review highlighted that most of the studies regarding LVFT were performed on a general population and documented a correlation with arrhythmias and structural cardiac disease, while only a few and dated investigations described the correlation with ventricular repolarization abnormalities[13] and no studies were conducted on healthy young athletes.

The purpose of this study was to describe the echocardiographic characteristics of LVFTs and their correlation with the abnormal ventricular ECG repolarization findings in a group of healthy young athletes.

MATERIALS AND METHODS

The study population was composed of 316 subjects (162 males and 154 females) with a mean age of 22.3 ± 4 years, consecutively evaluated from March 2009 to November 2011. All subjects were healthy and engaged in different agonistic sports disciplines (athletics, swimming, gymnastics, basketball, football and volleyball) for a total of approximately 15-20 h a week for about 8 mo a year.

All tested athletes had a negative medical family history and a normal baseline medical examination. In most cases (71%), auscultation sounds with the characteristics of a Still's murmur could be heard.

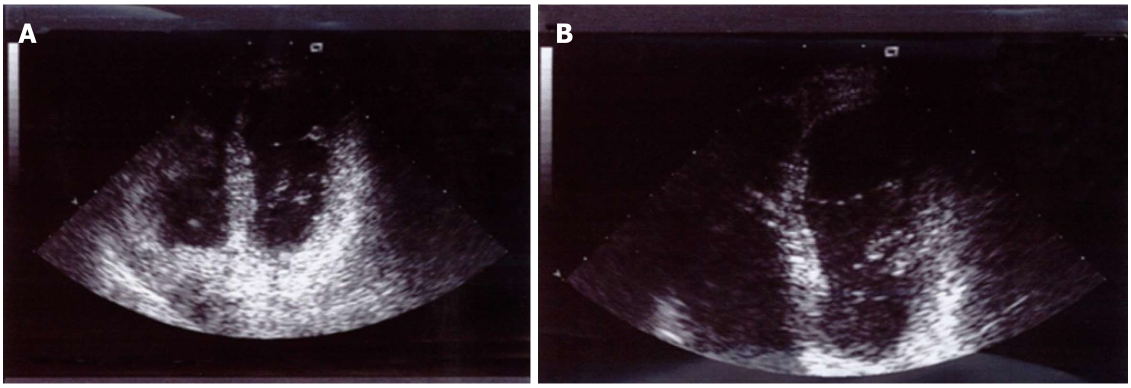

Figure 1 Left ventricular false tendon between the middle segments of the inferior septum and the lateral wall during the cardiac stolic (A) and diastolic (B) cycle.

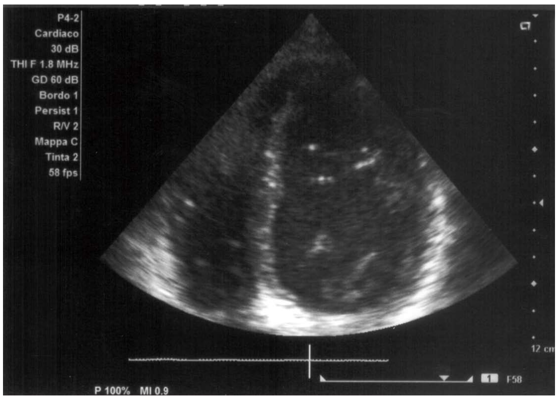

Figure 2 Double false tendon stretched between the lateral wall and inferior septum.

Each subject underwent: (1) a 12 lead ECG at rest and after a step test performed by the electrocardiographic device ESAOTE 421 ArchiMed-Esaote Biomedica. T wave flattening and the presence of T-wave inversion > 2 mm in one or more leads were considered for further investigations; (2) echocardiogram with bi-dimensional and color-Doppler evaluation using the instrument Terason T-3000 MORTARA. The echocardiographic diagnosis of false tendons in the left ventricle was based on the finding of a linear echogenic tendon, which crosses the left ventricular cavity, connecting different sites of the ventricular endocardium, and not correlated to the mitral valve apparatus. The false tendon size, thickness, pattern inside the left ventricular cavity, points of connection and tension or laxity during the cardiac cycle were evaluated; and (3) maximal exercise test on a cycle ergometer using the device Ergoline Ergometrics 800S and ECG monitoring device *via* CardiO2 MedGraphics, according to a protocol that included a 2 min warm-up at 20 W and subsequent increases of load for 40 W every 2 min, with active and passive recovery duration of 5 min. Values of systemic blood pressure and heart rate, during and after exercise were measured. Any cardiorespiratory symptoms and/or electrocardiographic changes during the execution of the test were noted.

Statistical analysis

Variables were reported by counts and percentages. When appropriate, comparisons were performed using a χ^2 test or Fisher's exact test. To evaluate the association between the variable of interest and the determinant, the odds ratio and 95% confidence interval (Cornfield's method) were calculated. All the tests were considered statistically significant for *P* values < 0.05. The analyses were conducted with STATA v.11.

RESULTS

Twenty one of the 316 subjects (6.9%), 12 males and 9 females with a mean age of 22 ± 2 years, showed false tendons in the left ventricle.

The majority of false tendons were localized between the middle segments of the inferior septum and the lateral wall (52.38%) (Figures 1 and 2), between the distal segments of the septum and the lateral wall (19.06%), between the middle segments of the anterior and inferior walls (23.8%), and between the middle segments of the anterior septum and the posterior wall (4.76%) (Table 1).

ECG abnormalities represented by alterations of ventricular repolarization were found in 11 subjects (52.38%).

The anomalies of the phase of ventricular repolarization observed in these cases were almost always characterized by the presence of inverted T waves from V1 to V3 (9 of 11 cases with abnormalities of the ventricular repolarization phase, 81%) (Figure 3).

Only one case had diphasic T waves from V1 to V3 and an inverted T wave in DIII and aVF. In this study, 90% of the anomalies of ventricular repolarization were abnormalities of the T wave from V1 to V3.

These anomalies disappeared with an increasing heart rate following three minutes of the step test as well as during the execution of the maximal exercise (Figure 4).

The association between false tendons in the left

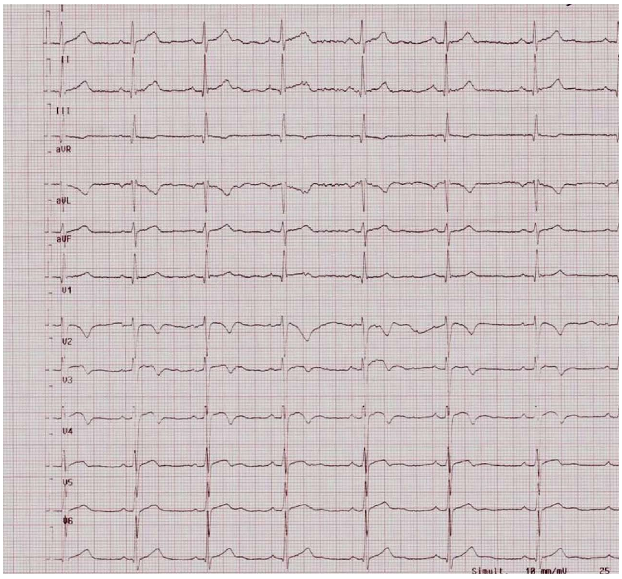

Figure 3 Ventricular repolarization anomalies in precordial leads V1-V4: Inverted T waves from V1 to V3 and flat T waves in D3.

ventricle and the abnormal ventricular repolarization phase showed an odds ratio of 11 (95%CI: 3.4-35.6, $P < 0.0001$).

The insertion sites of false tendons most often associated with abnormalities of the ventricular repolarization were in the middle segments of the inferior septum and the lateral wall (63.6%) and the distal segments of the septum and the lateral wall (30%). However, in this case, the Fisher's exact test did not demonstrate statistical significance ($P = 0.712$).

DISCUSSION

This study showed the presence of a statistically significant association between false tendons in the left ventricle and ventricular repolarization abnormalities. However, the odds ratio value is too high (a value of 11 with confidence interval width ranging from 3.4 to 3.5) due to the low number of subjects.

The false tendons were located more frequently (in over 63% of cases) between the middle segments of the interventricular septum and the lateral wall and presented a greater thickness when compared to normal tendons (> 2 mm). In 30% of cases, the false tendons stretched between the distal segments of the interventricular septum and the lateral wall.

The repolarization abnormalities were almost of the same type. Indeed, 90% of the subjects with a false tendon and an abnormal ventricular repolarization phase presented with alterations in T waves (more often reversed and symmetrical, sometimes diphasic) from V1 to V3.

The association between abnormalities of ventricular repolarization and false tendons in the left ventricle was described by Sutton *et al*[14] who presented three case reports regarding three patients in apparently good health with a false tendon in the left ventricle and inverted T waves in the precordial leads.

Table 1 Type of false tendon and altered ventricular repolarization

Anatomic site of false tendon	N° (%)	Altered ventricular repolarization N° (%)
Middle segment inferior septum - lateral wall	11 (52.38)	7 (63.6%)
Distal segment inferior septum - lateral wall	4 (19.06)	2 (50%)
Middle segment posterior wall - anterior septum	1 (4.76)	0 (0%)
Middle segment inferior wall - anterior wall	5 (23.8)	2 (40%)
Description of altered ventricular repolarization	Frequency	%
Flat T wave in DII, aVF, inverted T wave in DIII	10	47.6
Biphasic T wave in DII, DIII and aVF after incremental max exercise test	1	4.8
Biphasic T wave in V2 and V3, normalize after incremental max exercise test	1	4.8
Inverted T wave from V1 to V3 normalizes after incremental max exercise test	6	28.6
Inverted asymmetric T wave from V1 to V3 normalizes after incremental max exercise test	1	4.8
Inverted symmetric T wave from V1 to V3, that reduces but does not normalize after incremental max exercise test	1	4.8
Flat T wave in DIII and inverted from V1 to V3 normalizes after incremental max exercise test	1	4.8

Sutton *et al*[14] also noted an "electro-anatomical" correlation between false tendons and ECG abnormalities as well as the absence of modifications after a long follow-up of 13 years in his study. Other authors also identified the presence of Purkinje fibres within the false tendons; this information could explain the onset of arrhythmias associated with the presence of left ventricular false tendons. Some authors investigating the possible link between false tendons and ECG abnormalities identified 71 subjects with a false tendon and studied the possible presence of arrhythmias, such as ventricular extrasystole. The authors concluded that the false tendon can contribute to the etiology of arrhythmias such as ventricular extrasystole, but they did not describe abnormalities of the ventricular repolarization phase[15,16].

The statistically significant association between the presence of false tendons in the left ventricle and abnormal ventricular repolarization phase could have several explanations. The presence of a false tendon in the left ventricle would increase, although minimally, myocardial active mass, typical of the athlete's heart[10]. This increase in myocardial mass could activate a prolongation of the depolarization and eventually lead to T wave inversion. An alternative hypothesis considers purely mechanical aspects: the false tendon and its site of anatomical implantation (mainly medium-distal segments of the inferior septum and lateral wall) may exert mechanical traction

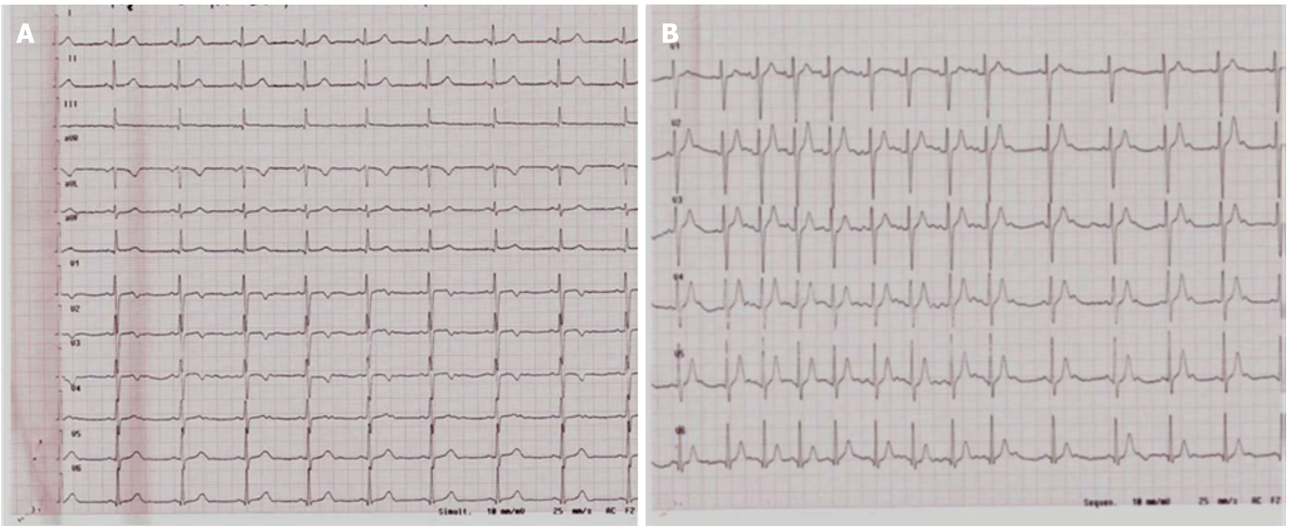

Figure 4 Ventricular repolarization anomalies at rest (A) and normalization after the incremental maximal exercise test on a cycle ergometer (B).

sufficient to alter repolarization.

Finally, the fibro-muscular false tendon contains elements of the cardiac conduction system, often providing the explanation for electrocardiographic abnormalities that might be associated with these structures[4].

In clinical practice, abnormal T-wave flattening and/or inversion can be detected in different physiological and pathological conditions[17]. When considering young and healthy subjects, T-wave flattening and/or inversion were found with variable frequency, from 0.5% to 19%, and in high-level athletes they have been described as clinically negative in 60%-80%[18]. The behavior of ventricular repolarization abnormalities during the incremental maximal exercise test on a cycle ergometer has fundamental importance. This test has significant diagnostic and prognostic importance. Usually, the normalization of T waves during a maximal exercise test on an ergometer suggests their benign nature, although in some cases organic diseases of the heart cannot be excluded[19] .

The results of this study showed a statistically significant association between the presence of false tendons in the left ventricle and ventricular repolarization abnormalities in a population of young healthy subjects engaged in competitive sports. The type of false tendon most frequently associated with ventricular repolarization abnormalities was identified in the middle-distal segments of the inferior interventricular septum and the lateral wall. Ventricular repolarization abnormalities of subjects with false tendons were all of the same type, indeed, the electrocardiogram showed inverted T waves from V1 to V3. These anomalies also regressed with the increase in heart rate during the physical exercise or incremental maximal exercise test on a cycle ergometer. A common electrocardiographic pattern can be described in athletes with a false left ventricular tendon. In fact, the ventricular repolarization abnormalities in the electrocardiogram in these individuals were similar and showed the same behavior under stress. The limitations of our study are related to the low number of participants and the lack of long term follow-up to evaluate eventual modifications.

In conclusion, the present study showed a statistically significant association between the presence of false tendons in the left ventricle and ventricular repolarization abnormalities in a population of young healthy subjects engaged in competitive sports.

The type of false tendon most frequently associated with ventricular repolarization abnormalities was identified among the middle-distal segments of the inferior interventricular septum and the lateral wall. Nonetheless, the results of this study may provide useful information for sports physicians when basic ECG abnormalities of ventricular repolarization are found.

COMMENTS

Background

False tendons are fibrous, fibrous-muscle or muscle structures, variable in length and thickness, found in the left ventricular cavity, generally located between the free wall of the left ventricle or a papillary muscle and the interventricular septum, without connection to the mitral valves. In 1893, Turner first described the false tendons in the left ventricle (LVFT) but the functional significance of these structures is still unclear. The left ventricular false tendons are easily identifiable with bi-dimensional echocardiography. They are usually found in 50% of autoptical examinations, mostly in males. Generally, LVFTs have been considered a normal variation but in some cases could be related to cardiac pre-excitation, ventricular arrhythmias, dilation of the left ventricle, congenital and/or acquired heart disease and some repolarization abnormalities on a resting electrocardiogram (ECG), including negative or diphasic T waves in precordial leads as well as early repolarization. Only a few studies have investigated the correlation between LVFTs and ventricular repolarization abnormalities and to our knowledge, no studies have been carried out on healthy young athletes. In this study they evaluated and described the echocardiographic characteristics of LVFTs and their correlation with the abnormal ventricular ECG repolarization findings in a group of healthy young athletes.

Research frontiers

The results of this study clarified the functional significance of left false tendons, adding useful information for the interpretation of abnormal ventricular ECG repolarization findings during the pre-participation screening of healthy athletes.

Innovations and breakthroughs

The present study describes a statistically significant association between the presence of false tendons in the left ventricle and ventricular repolarization abnormalities for the first time. This finding certainly provides useful information for sports medicine physicians for the interpretation of ECG abnormalities found in otherwise healthy athletes during the pre-participation screening evaluation.

Applications

This study provides useful information for sports physicians about sport eligibility evaluation for athletes when basic ECG abnormalities of ventricular repolarization are found.

Terminology

LVFTs: Fibrous, fibrous-muscle or muscle structures generally located between the free wall of the left ventricle or a papillary muscle and the interventricular septum, without connection to the mitral valves; ECG: Electrocardiogram; VRA: Ventricular repolarization abnormalities.

Peer-review

This is an interesting study that is well written and uses appropriate methods. It was suggested that another image demonstrating the LV false tendon should be provided as this is a key aspect of the study and should be better illustrated.

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P- Reviewer: Azevedo C, Jankowski P, Simkhovich B
S- Editor: Kong JX **L- Editor**: A **E- Editor**: Wu HL

World Journal of Cardiology

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4330/wjc.v8.i10.596

World J Cardiol 2016 October 26; 8(10): 596-605
ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Retrospective Study

Congenital coronary artery fistulas complicated with pulmonary hypertension: Analysis of 211 cases

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Author contributions: Said SAM has solely contributed to conception, design, drafting and final approval of the manuscript.

Institutional review board statement: The data of this manuscript are obtained from internet, so it should be excepted from approval of institutional review board.

Conflict-of-interest statement: Author has no conflict of interest in connection with the submitted article. No funding has been obtained.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at salah.said@gmail.com.

Manuscript source: Unsolicited manuscript

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Received: February 12, 2016
Peer-review started: February 16, 2016
First decision: March 23, 2016
Revised: July 26, 2016
Accepted: August 6, 2016
Article in press: August 8, 2016
Published online: October 26, 2016

Abstract

AIM

To compare the behavior of pulmonary hypertension (PHT) associated with coronary artery fistulas (CAFs) between the Asian and Caucasian subjects.

METHODS

CAFs may be complicated with PHT secondary to left-to-right shunt. Literature review limited to the English language. A total of 211 reviewed patients were collected. Of those, 111 were of Asian and 100 were of Caucasian ethnic origin. The mean age of the Asian and the Caucasian groups of patients were 48.9 (range 19-83) and 49.9 years (range 16-85), respectively. In both groups, right heart catheterization was the most commonly (95%) used method for determining pulmonary artery pressure.

RESULTS

From all of the reviewed subjects, PHT was found in 49 patients (23%), of which 15 were Asian and 34 were Caucasian. In 75% of PHT subjects, mild to moderate PHT was reported and 76% of the fistulas had a vascular mode of termination. Treatment was surgical in 61%, followed by percutaneous therapeutic embolization (27%) and finally conservative medical management in 12% of PHT subjects. PHT was associated with a slight female gender predominance. The majority demonstrated mild to moderate PHT. PHT was reported more frequent in the Caucasian compared with the Asian ethnicity group. The majority of fistulas in patients with PHT had a vascular mode of termination. The results of this review are intended to be indicative and require cautious interpretation.

CONCLUSION

The likelihood for a CAF patient to develop PHT is presented when possessing the following features, with a Caucasian female having a fistula with a vascular mode of termination.

Key words: Congenital coronary artery fistulas; Congenital anomaly; Pulmonary hypertension; Asian population; Caucasian population

Core tip: Congenital coronary artery fistulas (CAFs) are infrequent but hemodynamically important anomalies which may evolve a myriad of complications, such as myocardial infarction, congestive heart failure, infective endocarditis, aneurysm, rupture, pericardial effusion, arrhythmias and sudden death. In addition, secondary pulmonary hypertension (PHT) may complicate the course of CAFs. Moreover, when monitoring CAF patients, the clinicians responsible for the management of patients with congenital CAFs should be aware of the development of PHT during the course of the disease.

Said SAM. Congenital coronary artery fistulas complicated with pulmonary hypertension: Analysis of 211 cases. *World J Cardiol* 2016; 8(10): 596-605 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i10/596.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i10.596

INTRODUCTION

Congenital coronary artery fistulas (CAFs) are uncommon anomalies. Most CAFs are small and hemodynamically inconsequential with a negligible shunt. However, some can be sizeable and lead to shunting of blood from the coronary circulation to low-pressure pulmonary vascular bed, resulting in pulmonary hypertension (PHT)[1]. CAFs may be associated with normal[2-4] pulmonary artery pressure (PAP) in unilateral[5-8] or bilateral[9,10] fistulas, or may sometimes be accompanied with elevated PAP[11-14]. Rarely, in octogenarians with bilateral CAFs, PAP may remain normal[15].

The hemodynamic consequences of CAFs varies, depending on their magnitude and the cardiac chamber or vascular site involved. Fistulas terminating into the right heart chambers may produce left-to-right shunt and volume overload of the pulmonary circulation, whereas fistulas to the left heart side cause left ventricular volume overload.

In a literature review, 211 subjects were included and a comparison was made between the Asian (*n* = 111) and Caucasian (*n* = 100) subjects regarding the behavior of PAP associated with CAFs.

MATERIALS AND METHODS

The data source was based on an extensive literature review of the English literature in the PubMed database regarding congenital CAFs and PAP. The search was conducted using the terms "congenital coronary artery fistulas" and "pulmonary artery pressure". Inclusion of a paper occurred when full data on PAP either using right heart catheterization (RHC) (direct measurement) or Doppler echocardiography [calculation of estimated PAP based on tricuspid regurgitation (TR) peak velocity] were provided.

This retrieval resulted in a collection of 133 papers which included 49 of Asian (*n* = 111 patients) and 84 of Caucasian (*n* = 100 patients) reports. Three were excluded because of duplication. Reference lists from selected papers were manually searched for potentially relevant publications. Whenever available, the most recent data were included. Another seven papers were therefore added, meaning that the final retrieval result was 137 papers. Congenital multiple micro-fistulas were not included and patients with acquired fistulas were excluded.

Definition of PHT[16-18]

Invasive method: PHT is defined as the systolic PAP (sPAP) or mean PAP, exceeding 35 mmHg or 25 mmHg, respectively. Furthermore, the mean PAP rises above 30 mmHg with exercise, occurring secondary to either a pulmonary or a cardiac disorder[16].

Non-invasive method: In accordance with the European Society of Cardiology criteria for detecting the presence of PHT, based on the TR peak velocity and Doppler-calculated sPAP at rest (assuming a normal right atrial pressure of 5 mmHg), additional echocardiographic variables suggestive of PHT were used to determine the sPAP[19,20]. PHT was defined by an estimate of right ventricular systolic pressure of greater than 40 mmHg. sPAP is estimated using TR jet velocity based on the simplified Bernoulli's equation [$4 \times (TRV)^2$ + RA pressure][19,21,22] (TRV: TR velocity; RA: Right atrium). PHT was classified into three categories: Mild (40-49 mmHg), moderate (50-59 mmHg) and severe (> 59 mmHg).

Statistical analysis

Values were expressed as means, averages, and percentages.

RESULTS

Total group

A total of 211 (M: 87 = 41% and F: 124 = 59%) reviewed patients were collected from the world literature. The mean age was 49.4 years (range 16-85). The reported method of assessment of PAP was RHC (*n* = 201, Caucasian *n* = 94 and Asian *n* = 107) and Doppler echocardiography (*n* = 10, Caucasian *n* = 6 and Asian *n* = 4) in 95% and 5% of the subjects, respectively. The congenital CAFs were unilateral in 118 (56%), bilateral in 87 (41%) and multilateral in 6 (3%) of the subjects. The CAFs arose from the right (133/268 = 49.6%) and left (135/268 = 50.4%) coronary artery, respectively. The mode of termination was either vascular (90/211 =

Table 1 Reviewed Asian (n = 111) and Caucasian (n = 100) group of patients

	Total reviewed subjects	Asian group	Caucasian group
n	211	111 (53%)	100 (47%)
Gender	F 124 (59%)	F 63 (57%)	F 61 (61%)
	M 87 (41%)	M 48 (43%)	M 39 (39%)
Mean age (range)[1], yr	49.4 (16-85)	48.9 (19-83)	49.9 (16-85)
CAF characteristics			
Unilateral	118 (56%)	42 (38%)	76 (76%)
Bilateral	87 (41%)	63 (57%)	24 (24%)
Multilateral	6 (3%)	6 (5%)	-
Mode of termination			
CVFs	90 (43%)	43 (39%)	47 (47%)
CCFs	121 (57%)	68 (61%)	53 (53%)
RHC	201 (95%)	107 (96%)	94 (94%)
sPAP/RVSP	10 (5%)	4 (4%)	6 (6%)
Management			
CMM	38	20	18
PTE[2]	29	9 (8%)	20 (20%)
SL	124 (59%)	82 (74%)	42 (42%)
WW	2	-	2
Death	2	-	2
Not mentioned	16	-	16

[1]Subjects (n = 41) from ref. [35] were not included in calculation of mean age (n = 170, 70 Asian and 100 Caucasian). [2]In one patient, PTE failed followed by SL treatment (ref. [147]) and another treated with hybrid procedures (ref. [133]). CAF: Coronary artery fistula; CCFs: Coronary-cameral fistulas; CVFs: Coronary-vascular fistulas; CMM: Conservative medical management; F: Female; M: Male; PTE: Percutaneous therapeutic embolization; RHC: Right heart catheterization; SL: Surgical ligation; sPAP: Systolic pulmonary artery pressure; RVSP: Right ventricular systolic pressure.

43%) or cameral (121/211 = 57%) (Table 1).

Among the applied therapeutic modalities, surgical ligation (SL) was performed in 124 (59%), conservative medical management (CMM) in 38 (18%), percutaneous therapeutic embolization (PTE) in 29 (13%) and watchful waiting in 2 (1%). There were 2 mortalities (1%) and treatment options were not mentioned in 16 (8%) of the subjects. Among the whole group, 23% (49/211) were found to have elevated PAP.

Asian population: *n* = 111

The reviewed patients of Asian ethnicity [n = 111, Male n = 48 (43%) and Female n = 63 (57%)] had a mean age of 48.9 years (range 19-83).

Between 1986 and 2014, papers published describing Asian population with congenital CAFS and reported data on PAP were included: from 1986-1993[23-28], 1994-1999[29-33], 2001-2004[34-39], 2005[40-42], 2006[43-49], 2007[50-55], 2009-2011[56-61] and 2012-2014[62-69]. PAP was measured by RHC in 107 and by Doppler echocardiography in 4.

Ninety-six subjects (86%) had normal PAP. Among the CAFs, 42 were unilateral (38%), 63 bilateral (57%) and 6 multilateral (5%). The treatment modalities were SL [82 = (74%)], CMM [20 = (18%)] and PTE [9 = (8%)]. No watchful waiting strategy was conducted and death did not occur in any of the subjects.

Table 2 Asian and Caucasian group of patients (n = 49) with pulmonary hypertension

	Total group	Asian group	Caucasian group
n	49	15 (31%)	34 (69%)
Age[1]	56 (16-80)	54.4 (24-77)	56.8 (16-80)
Gender	F 34 (69%)	F 12 (80%)	F 22 (65%)
	M 15 (31%)	M 3 (20%)	M 12(35%)
CAF			
Unilateral	37 (76%)	9 (60%)	28 (82%)
Bilateral	12 (24%)	6 (40%)	6 (18%)
PHT			
Mild	26 (53%)	8/15 (53%)	18/34 (53%)
Moderate	11 (22%)	2/15 (13%)	9/34 (26%)
Severe	12 (25%)	5/15 (33%)	7/34 (21%)
Mean PAP (mmHg)	35.6 (range 26-60)	36.9 (range 27-49)	34.3 (range 26-60)
Mean Qp:Qs ratio	1.9 (range 1.13-2.75)	1.9 (range 1.13-2.75)	1.9 (range 1.3-2.7)
RHC	43 (88%)	13 (87%)	30 (88%)
Doppler (sPAP)	6 (12%)	2 (13%)	4 (12%)
CAF characteristics			
Origin	R 8, L 30, bilateral 11	R 2, L 8, bilateral 5	R 6, L 22, bilateral 6
Termination	RH side 45 LH side 4	RH side 13 LH side 2	RH side 32 LH side 2
Mode of termination			
CVFs	37 (76%)	9/15 (60%)	28/34 (82%)
CCFs	12 (24%)	6/15 (40%)	6/34 (18%)
Associated disorders	17/49 (35%)	5/15 (33%)	12/34 (35%)
Management			
SL	30 (61%)	9	21
PTE	13 (27%)	4	9[2]
CMM	6 (12%)	2	4

[1]Subjects from ref. [35] were not included in calculation of mean age. Mean age was calculated from 170 (70 Asian and 100 Caucasian) subjects. [2]One PTE failed (from ref. [147]) followed by SL treatment and another treated with hybrid procedures (from ref. [133]). CAF: Coronary artery fistula; CCFs: Coronary-cameral fistulas; CVFs: Coronary-vascular fistulas; CMM: Conservative medical management; F: Female; R: Right coronary artery; L: Left coronary artery; LH: Left heart side; M: Male; PAP: Pulmonary artery pressure; PHT: Pulmonary hypertension; PTE: Percutaneous therapeutic embolization; RH: Right heart side; RHC: Right heart catheterization; SL: Surgical ligation; sPAP: Systolic pulmonary artery pressure.

PHT was found in 15 Asian (14%) (M, n = 3; F, n = 12) subjects with a mean age 54.4 years (range 24-77). Among the 15 subjects, mild, moderate and severe PHT was detected in 8, 2 and 5, respectively.

Caucasian population: n = 100

The mean age (n = 100, Male 39 and Female 61) was 49.9 years (range 18-85). Published papers on Caucasian population regarding CAFs and PAP between 1955 and 2014 were included for evaluation: 1955-1961[70-75], 1964-1967[5,76-78], 1971-1976[2,79-82], 1981-1989[11,83-85], 1990-1991[3,6,10,86,87], 1992-1994[88-92], 1995-1997[4,9,31,93-95], 2000-2002[12,13,96-101], 2003-2004[102-106], 2005-2006[7,15,107-113], 2007-2009[14,114-124], 2010-2012[8,125-130], and 2013-2014[131-134]. PAP was evaluated by RHC in 94% (n = 94) and in 6 by Doppler echocardiography method. The CAFs were unilateral in 76 (76%) and bilateral in 24 (24%) of the subjects. No multilateral fistulas were reported. Sixty-six subjects (66%) had normal PAP.

Treatment modalities included SL (42), PTE (20), CMM (18), and watchful waiting (2), and were not mentioned in 16 cases. There were 2 mortalities (2). PHT was found in 34 subjects (34%) [M: n = 12 (35%) and F: n = 22 (65%)], with a mean age of 56.8 years (range 16-80).

PHT population: n = 49

PHT was found in 49 patients (49/211 = 23%), with a mean age of 56 years (range 16-80). There were 34 females (69%) and 15 males (31%), with 15 Asian (mean age 54.4, range 24-77 years) and 34 (mean age 56.8, range 16-80 years) of Caucasian patients. The fistulas were unilateral in 37 (76%) and bilateral in 12 (24%) of the subjects. Measurement of PAP was achieved by RHC in 43 subjects (13 Asian and 30 Caucasian) and by Doppler echocardiography in 6 (2 Asian and 4 Caucasian) subjects. Mild, moderate and severe PHT was reported in 26 (53%), 11 (23%) and 12 (24%) subjects, respectively (Table 2).

The following features were detected among PHT group of patients: A female predominance (34/49 = 69%), unilateral origin (37/49 = 76%) from the left coronary artery (30/49 = 61%) and termination into the right heart side (45/49 = 92%) were the major findings of the PHT group of patients.

The percentage of unilateral and CVFs was higher in the Caucasian group (82% and 82%) compared to the Asian group (60% and 60%), respectively (Table 3).

DISCUSSION

CAFs may remain silent, co-existing with longevity for years and emerging as a coincidental finding during non-invasive or invasive[135] investigation for the analysis of suspected cardiac disorder.

CAFs are an uncommon congenital anomaly which may be associated with several complications (Table 4). These complications may have coronary vascular, pericardial or myocardial origin. Furthermore, they may have a valvular source or may originate from an atrial or ventricular arrhythmic substrate. Such complications may include myocardial infarction (MI) (4%)[136,137], congestive heart failure (20%)[136], infective endocarditis (reported in 4%-12% in different series)[81,136], atrial[138] and ventricular[139] arrhythmias, aneurysm (reported in 20% of cases)[96,140], rarely ruptured aneurysm with hemopericardium[141] and unruptured aneurysm[139,142], pericardial effusion[143], syncope[142,144] and sudden death[145]. It has been postulated that fistula-related complications increase with age[136]. Secondary PHT is an infrequent complication of congenital CAFs. As early as 1955, Davison reported PHT in patients with CAFs[70].

Most CAFs are small and hemodynamically inconsequential with a negligible left-to-right shunt. However, some can be sizeable and lead to shunting of blood from the coronary circulation to low-pressure pulmonary vascular bed, resulting in PHT[1].

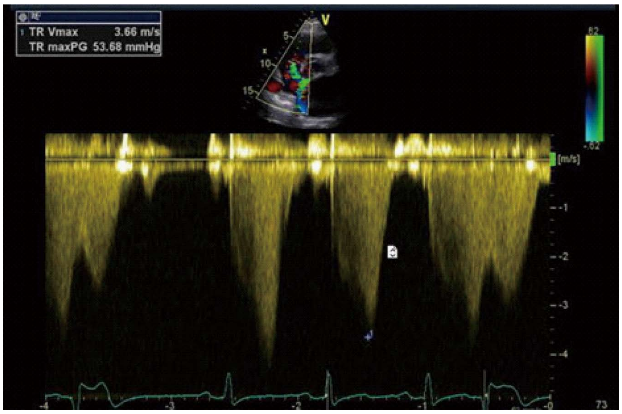

Figure 1 Continuous wave Doppler demonstrating blood flow velocity (3.66 m/c) across the tricuspid valve.

In congenital CAFs, although PHT may occur when sizeable left-to-right shunt exists; in the current review, the mean Qp:Qs was modest, with moderate magnitude 1.9:1.0.

It has been stated that severe PHT is not frequently observed in isolated CAFs[87]. Mild to moderate PHT[5] has sporadically been reported in unilateral[39,45,107,124,146,147] and bilateral fistulas[42,103,112,118]. Indeed, in the current literature review, only 25% were found to have severe PHT, with the majority (75%) having mild or moderate PHT. No reports of multilateral CAFs associated with PHT were found. It is noteworthy that CAFs may be associated with longevity[96] and PHT has been reported in septuagenarians[11] and octogenarians[107].

Although PAP can be measured on Doppler echocardiography, the gold standard for diagnosis is RHC. In the current review, 95% were direct calculation of PAP using RHC and only 5% as an estimate of right ventricular systolic pressure by Doppler echocardiography using TR jet velocity based on the simplified Bernoulli's equation (Figure 1). It is widely accepted that pulmonary artery systolic pressure (sPAP) can be considered normal until 40 mmHg in the elderly and obese subjects. Moreover, tricuspid regurgitant jet velocity is a parameter that has been widely applied to estimate sPAP[22].

In comparison with the Caucasian group of patients (65%) with PHT, female gender accounted for 80% in the Asian group and was almost equally associated (35% *vs* 33%) with concomitant congenital and acquired coronary and valvular heart defects.

In the total group of patients (n = 49) with PHT, female gender accounted for (69%), unilateral fistulas was present in (76%) and mild to moderate PHT (75%) was predominant. RHC was performed in 88% of patients and in 12% Doppler echocardiography was used for estimation of the sPAP. Coronary vascular fistulas as a mode of termination were found in the overwhelming majority (76%) of patients. SL was performed in 61% of

Table 3 Mode of termination coronary-vascular fistulas *vs* coronary-cameral fistulas in the pulmonary hypertension (n = 49) and all reviewed (n = 211) subjects

	CVFs	CCFs	Mean age and range (yr)
Total n = 211	90/211 (43%)	121/211(57%)	38.3 (26-67)
Asian 15/111 (14%)	9/15 (60%)	6/15 (40%)	39.7 (27-67)
Caucasian 34/100 (34%)	28/34 (82%)	6/34 (18%)	36.8 (26-60)

CCFs: Coronary-cameral fistulas; CVFs: Coronary-vascular fistulas.

Table 4 Possible complications of coronary artery fistulas

Complication	Features
Cardiovascular	Myocardial infarction, stroke, aneurysm, rupture
Infectious	Bacterial endocarditis, septic pulmonary and septic renal embolism
Valvular	Incompetence, dysfunction, perforation
Pericardial	Hemopericardium, pericardial effusion, tamponade
Myocardial	Congestive heart failure
Arrhythmic	Supraventricular arrhythmias, ventricular arrhythmias and sudden death

patients with PHT.

In the present review of all 49 subjects, possible common features of CAFs associated with PHT were unilateral fistula (37/49 = 76%) originating from the left coronary artery (30/49 = 61%) with a vascular termination (76%) into the right heart side (45/49 = 92%). These findings have to be investigated in a future international survey or prospective study.

A significant difference was noted in the percentages of coronary-cameral fistulas between Asian (40%) and Caucasian (18%) groups of patients with PHT. There was no difference in associated cardiac defects, congenital or acquired, in both the Asian and Caucasian groups (33% and 35%, respectively).

Limitations of the study

Among the Asian population reported by Cheung *et al*[35] in 2001, among the 41 subjects, there were children included in their study. The time span for data collection spread from 1955 to 2014 due to period collection bias.

Publication bias, only subjects with abnormal findings are accepted for publication. Although the data were of high quality and were collected from the world literature, the results of this review are intended to be indicative and require cautious interpretation.

It is clear that more research and studies are warranted for the identification and registration of congenital CAFs associated with PHT; the cause seems to be more multi-factorial (gender, fistula origin and outflow) and dependent on the fistula characteristics itself. We are encouraged to initiate an international survey on CAFs (Euro-CAF.care).

In conclusion, among the whole population, 23% were found to have elevated PAP. In the Asian group of patients 14% demonstrated PHT compared to 34% among the Caucasian group. Among the patients (n = 49) with PHT, 69% were female. The majority of fistulas (76%) in patients (n = 49) with PHT were of CVFs type in contrast to CCFs who accounted for 24% of subjects. The likelihood for a CAF patient to develop PHT is presented when possessing the following features, with a Caucasian female having a fistula with a vascular mode of termination. The findings of this review need to be confirmed in a larger multicenter international registry, preferably with a longer follow-up.

ACKNOWLEDGMENTS

With gratitude the author wishes to thank the librarians of Hospital Group Twente, Mrs. A. Geerdink and Mrs. L. Gerritsen for their assistance during the preparation of the manuscript.

COMMENTS

Background

Congenital coronary artery fistulas (CAFs) are uncommon anomalies. Most CAFs are small and hemodynamically inconsequential with a negligible shunt. However, some can be sizeable and lead to shunting of blood from the coronary circulation to low-pressure pulmonary vascular bed, resulting in pulmonary hypertension (PHT).

Research frontiers

CAFs may be associated with normal pulmonary artery pressure (PAP) in unilateral or bilateral fistulas, or may sometimes be accompanied with elevated PAP. Rarely, in octogenarians with bilateral CAFs, PAP may remain normal.

Innovations and breakthroughs

The likelihood for a CAF patient to develop PHT is presented when possessing the following features, with a Caucasian female having a fistula with a vascular mode of termination.

Applications

The findings of this review need to be confirmed in a larger multicenter international registry, preferably with a longer follow-up.

Peer-review

This paper is interesting review concerning association PAH and CAF. Therefore, this article should be published.

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P- Reviewer: Cebi N, Kettering K, Peteiro J **S- Editor**: Kong JX **L- Editor**: A **E- Editor**: Wu HL

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DOI: 10.4330/wjc.v8.i10.606

World J Cardiol 2016 October 26; 8(10): 606-614
ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Clinical Trials Study

Optimal C-arm angulation during transcatheter aortic valve replacement: Accuracy of a rotational C-arm computed tomography based three dimensional heart model

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Author contributions: Veulemans V, Mollus S contributed equally to this study as primary authors; Veulemans V, Mollus S and Balzer J designed the study, analyzed and interpreted data and wrote the manuscript; Saalbach A, Pietsch M, Hellhammer K, Zeus T, Westenfeld F, Weese J and Kelm M supervised the study and revised the manuscript.

Institutional review board statement: The study conformed to the Declaration of Helsinki and was accepted by the University of Düsseldorf Ethics Committee.

Clinical trial registration statement: This registration policy applies to registry trials. https://clinicaltrials.gov/ct2/show/NCT01805739.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment, titled "Multi Modal Cardiac Imaging Prior Transcatheter Aortic Valve Implantation".

Conflict-of-interest statement: Tobias Z and Verena V receive honoraria from St. Jude Medical for lectures. Philips Healthcare and the University Hospital Duesseldorf have a master research agreement. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

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Received: May 8, 2016
Peer-review started: May 9, 2016
First decision: June 13, 2016
Revised: July 23, 2016
Accepted: August 30, 2016
Article in press: August 31, 2016
Published online: October 26, 2016

Abstract

AIM

To investigate the accuracy of a rotational C-arm CT-based 3D heart model to predict an optimal C-arm configuration during transcatheter aortic valve replacement (TAVR).

METHODS

Rotational C-arm CT (RCT) under rapid ventricular pacing was performed in 57 consecutive patients with severe aortic stenosis as part of the pre-procedural cardiac catheterization. With prototype software each RCT data set was segmented using a 3D heart model. From that the line of perpendicularity curve was obtained that generates a perpendicular view of the aortic annulus according to the right-cusp rule. To evaluate the accuracy of a model-based overlay we compared model- and expert-derived aortic root diameters.

RESULTS

For all 57 patients in the RCT cohort diameter measurements were obtained from two independent operators and were compared to the model-based measurements. The inter-observer variability was measured to be in the range of 0°-12.96° of angular C-arm displacement for two independent operators. The model-to-operator agreement was 0°-13.82°. The model-based and expert measurements of aortic root diameters evaluated at the aortic annulus (r = 0.79, P < 0.01), the aortic sinus (r = 0.93, P < 0.01) and the sino-tubular junction (r = 0.92, P < 0.01) correlated on a high level and the Bland-Altman analysis showed good agreement. The interobserver measurements did not show a significant bias.

CONCLUSION

Automatic segmentation of the aortic root using an anatomical model can accurately predict an optimal C-arm configuration, potentially simplifying current clinical workflows before and during TAVR.

Key words: Aortic stenosis; Imaging modalities; Degenerative valve disease; Transcatheter aortic valve replacement

Core tip: We were able to demonstrate the accuracy of a rotational C-arm CT (RCT) based 3D heart model to predict an optimal C-arm configuration and to provide anatomical context information during transcatheter aortic valve replacement (TAVR). Established and upcoming complex cardiac interventions require detailed anatomical information for procedure planning and intra-procedural guidance. According to our experience, RCT can be smoothly integrated into the clinical workflow, providing three-dimensional information of the relevant anatomical structures in the catheterization lab prior and as part of the TAVR intervention.

Veulemans V, Mollus S, Saalbach A, Pietsch M, Hellhammer K, Zeus T, Westenfeld R, Weese J, Kelm M, Balzer J. Optimal C-arm angulation during transcatheter aortic valve replacement: Accuracy of a rotational C-arm computed tomography based three dimensional heart model. *World J Cardiol* 2016; 8(10): 606-614 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i10/606.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i10.606

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is an established treatment option for patients ineligible for surgery that suffer from severe aortic stenosis[1,2]. Optimal positioning of the prosthetic valve during the intervention in the catheter laboratory is crucial for procedural success. Malpositioning may lead to valve embolization, coronary ostial obstruction, perivalvular regurgitation, or conduction disturbances[3]. Optimal and safe device deployment is best accomplished by generating a specific fluoroscopic view perpendicular to the annulus plane, also known as the line of perpendicularity (LP)[4]. To achieve this specific fluoroscopic view during the TAVR procedure, several angiograms in different angulations of the C-arm are necessary, causing a considerable amount of nephrotoxic contrast agent and radiation for the patient and the operator[5]. Therefore, an accurate definition of the aortic annulus and the LP is desirable before the procedure is performed. Today, MSCT is the preferred modality for TAVR planning and intervention guidance, providing information about anatomic conditions as well as the opportunity to reformat the reconstruction in any 3D orientation[6,7].

Different imaging techniques have been established to define the LP optimal fluoroscopic view during the preprocedural screening of patients. For angiography and MSCT[7-10] different software solutions for optimal view planning and their clinical benefits have been proposed. Automated view planning along the LP has shown to improve the quality of implantation, may speed up workflow and may reduce the need for low-dose aortograms[5]. Rotational C-arm computed tomography (RCT)-based view planning has proven to be of equal quality as MSCT-based techniques[10-12]. But current studies purely rely on non-quantitative evaluations and systematic validation of software-based methods is lacking.

In this study we therefore sought to (1) evaluate the accuracy of a RCT based 3D heart model for segmentation of the aortic root to predict an optimal C-arm configuration that generates a perpendicular view of the aortic annulus during TAVR and (2) investigate whether the accuracy of a RCT-specific model is suitable for intervention guidance, comparing the dimensions of an automatically derived overlay with manual reference measurements.

MATERIALS AND METHODS

Study population

Retrospectively, 57 consecutive patients (30 male, mean age 80.9 years) with symptomatic severe aortic stenosis that underwent cardiac catheterization with RCT prior to planned TAVR or surgical aortic valve replacement (SAVR) procedure have been selected. Patients with insufficient RCT image quality, *e.g.,* due to incomplete RVP (n = 2), delayed contrast timing (n

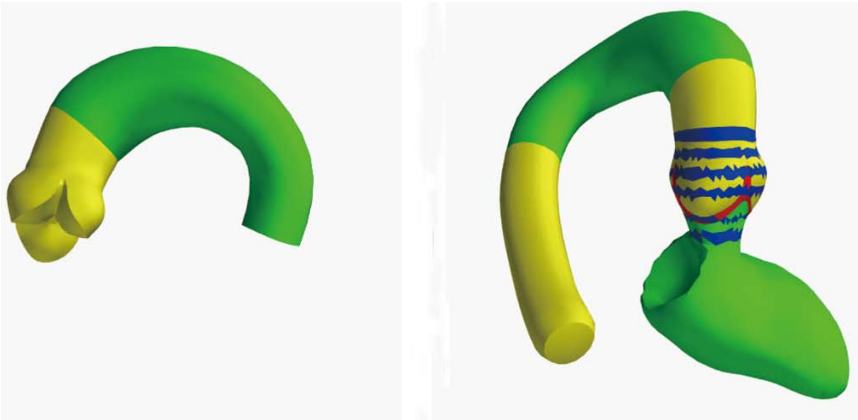

Figure 1 Mesh topology of the rotational C-arm computed tomography model for transcatheter aortic valve replacement (left), extended topology model with rings for diameter measurements (blue), prolonged descending aorta and left ventricle.

= 2), massive artefacts by ICD (*n* = 2) were excluded beforehand. All patients gave written consent and the study was approved by the local ethics committee (Study No. 4080, international registration NCT01805739).

RCT acquisition

RCT was performed as part of the pre-implant diagnostic coronary angiography study[13]. The C-arm of the Cathlab system (Allura FD 20, 30 cm flat panel detector, XperCT option, Philips Healthcare, Andover, MA, United States) was rotated over an angular range of 210° with a sweep duration of 5.2 s and a frame-rate of 60 frames/s around the patient. To mitigate motion the acquisition was conducted during inspiratory breath hold and under RVP. Contrast medium (Accupaque 350, Bracco Imaging, Konstanz, Germany) was diluted 1:1 with saline to a total volume of 0.8 mL/kg patient's weight (50-80 mL) and administered with a flow rate of 14 mL/s. The contrast agent was injected *via* a pigtail catheter either supravalvular into the ascending aorta aortic root or subvalvular into the left ventricular cavity. The rotational sweep data was reconstructed with standard product settings to a volume of size 256 × 256 × 198 with an isotropic resolution of 0.98 mm^3. Since the RCT acquisitions were performed during RVP the exact cardiac phase cannot be specified.

Expert-based data analysis

To assess the operator-variability and the accuracy of software-based optimal C-arm configurations, reference views were defined by a medical expert. Three-dimensional reconstructions of the RCT were visualized as multi-planar reformats with proprietary prototype software. Two blinded operators, experienced in the analysis of cardiac cross sectional imaging, used standard volume interaction techniques to manually define a view perpendicular to the aortic valve plane with respect to a reference viewport. From this optimal view, a LP curve was automatically derived using the mathematical definitions below and the result was presented to the user. Based on the LP curve and a volume rendering of the original RCT data set, the operators defined an optimal C-arm configuration in terms of rotation and angulation following the right-cusp rule[14].

Furthermore the RCT data sets were studied with vendor-independent image processing software (Osirix MD Ver. 4.0, pixmeo, Geneva, Switzerland). Two independent, blinded observers performed aortic root diameter measurements in multiplanar reformatted RCT data sets at the level of the aortic annulus, the aortic sinus and the sino-tubular junction (STJ). These are supposed to be representative for the shape and dimension of the aortic root anatomy to be overlaid to the fluoroscopic data stream for intervention guidance[13].

Model-based data analysis

For automatic view planning and intervention guidance in RCT, a model-based segmentation technique was employed[15]. Unlike other segmentation techniques, model-based segmentation integrates information about the typical shape of the target anatomy, its variability and appearance in the adaptation process, and has been successfully employed in a broad range of medical image processing applications[16-18]. To tailor the shape model to the image characteristics of RCT the model was trained on the 57 patients of the RCT cohort whereby the validation was set-up in a leave-N-out manner so that training and test set never coincided. The shape model covers the 3D outline of the aortic valve, the supravalvular part of the aorta, the aortic arch, a list of anatomical landmarks and rings encoded on the mesh model that enable geometrical measurements relevant for the TAVR application (Figure 1). For clinical validation each RCT data set was segmented with our prototype software using the 3D heart model. The aorta, the aortic valve and the left ventricle (if visible in the RCT data set) as well as the nadir landmarks of the three aortic valve cusps were extracted. From that, the LP curve was obtained and an optimal view that aligns the nadir landmarks according to the right-cusp rule was computed.

To compute the accuracy of the model-based overlay for intervention guidance we assume that the shape and the dimensions of the aortic root can be roughly

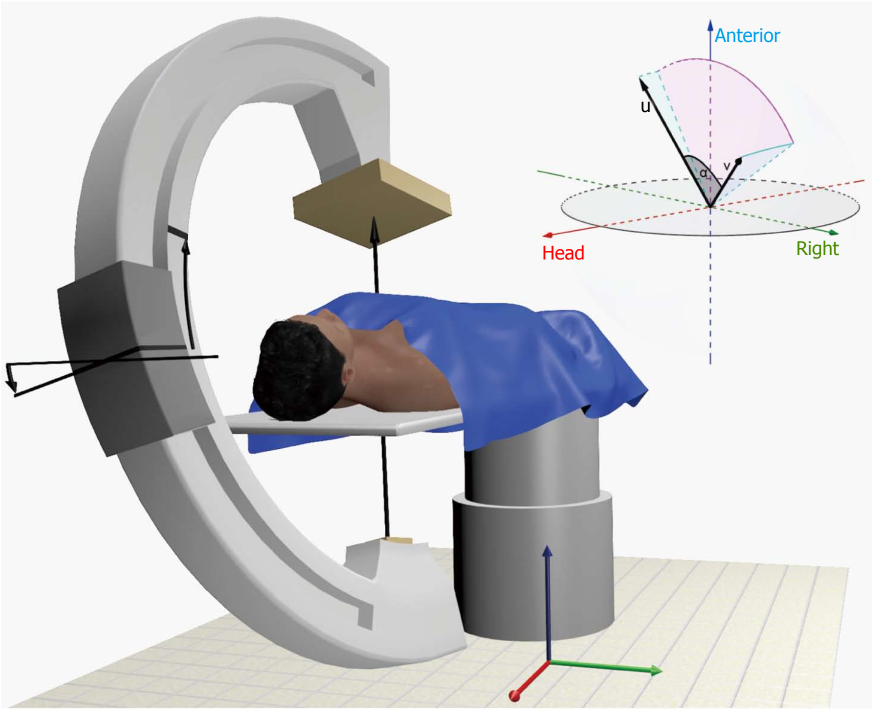

Figure 2 Definition of C-arm coordinate system and illustration of angular displacement between two position vectors each representing a C-arm projection view.

represented by a set of diameter measurements. These diameter measurements use the rings encoded on the segmentation model and are defined in accordance with the recommendations of the manufacturers of the TAVR devices. For the diameter of the annulus a circular cross-section model is fit to the segmentation result. The measurement of the bulbus width and the diameter of the STJ rely on an elliptical cross-section model.

Mathematical calculations and statistical analysis

The computation of the LP curve and the error computations require several geometrical definitions. Prerequisite is a Cartesian coordinate system which is defined in analogy to the work of Wollschläger *et al*[19]. The origin of the coordinate system coincides with the isocenter of the C-arm system. As in Figure 2 indicated, the C-arm can be angulated along the x-axis in cranial and caudal direction of the supine patient and is able to rotate along the y-axis in LAO and RAO direction. The z-axis is defined in dorsal-ventral patient orientation. One pair of rotation and angulation denoted as (ϕ,θ) can be represented by a vector in the C-arm coordinate system $v\_(\phi,\theta) = (x, y, z)$ where $x = \sin(\theta)$, $y = \sin(\phi)\cdot\cos(\theta)$, $z = \cos(\phi)\cdot\sin(\theta)$. Each combination of rotation and angulation spans a virtual half-sphere around the patient. In this half-sphere the LP curve is represented as trace of C-arm rotation and angulation combinations. Each respective view along this trace is orthogonal to the axial plane of the patient's aortic valve which can be defined by the unit vector $v\_AV = (x\_AV, y\_AV, z\_AV)$. To compute the LP curve we seek for a given C-arm rotation θ the C-arm angulations ϕ so that the vectors $v\_(\phi,\theta)$ and v_AV are perpendicular. This can be expressed as inner product of two vectors which is set to zero $v\_(\phi,\theta)\cdot v\_AV = 0$.

To evaluate the inter-observer variability and the agreement between model-based and expert-defined optimal views we compute the angular deviation (AD) between the respective position vectors v_model and v_expert in the spherical C-arm coordinate system which can be expressed as $\alpha = \text{acos}(v\_model \times v\_expert)$. In analogy to the work of the Tzikas-group[8], we compute the mean absolute difference and the standard deviation of the angular deviations between the position vectors given by the operators and the RCT model for all patients. However, this form of statistical analysis is error-prone, since it assumes the normal distribution of the random samples. But the angulation and rotation parameters are dependent on each other and further numerical restrictions (such as pole of acos-function near the optimal vector configuration) have to be considered. Thus, we propose to use a more advanced method of error calculation well-known from other research fields[20]. Therefore we apply Monte-Carlo methods to compute the cumulative distribution function of the angular deviations and use the value at 95% confidence level for the error calculation.

The Bland-Altman method was used for the assessment of the bias and standard deviations between model-based and expert-based aortic root measurements in RCT at 95% level of agreement (LoA). In addition, the Pearson correlation coefficient r was computed and t statistics were used to test the hypothesis of no correlation considering a significance level of $p < 0.01$. All statistical calculations were performed using Matlab Statistics Toolbox™ (MathWorks, Inc, Natick,

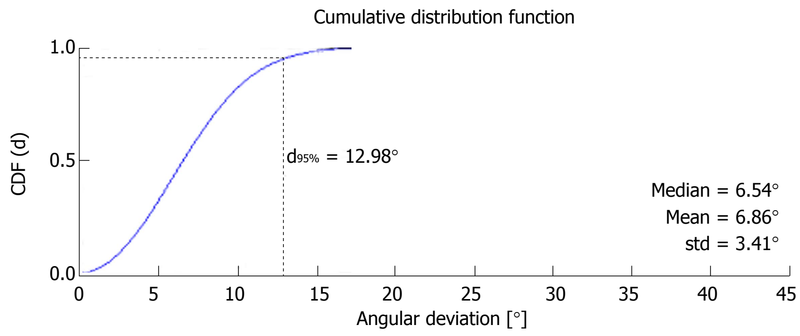

Figure 3 Interobserver variability of rotational C-arm computed tomography-based view planning. Using Monte-Carlo methods the cumulative distribution function of the angular deviation between two operator-defined C-arm configurations was computed; from this distribution function the expected angular deviation is derived to be the value of the distribution function at 95% confidence level.

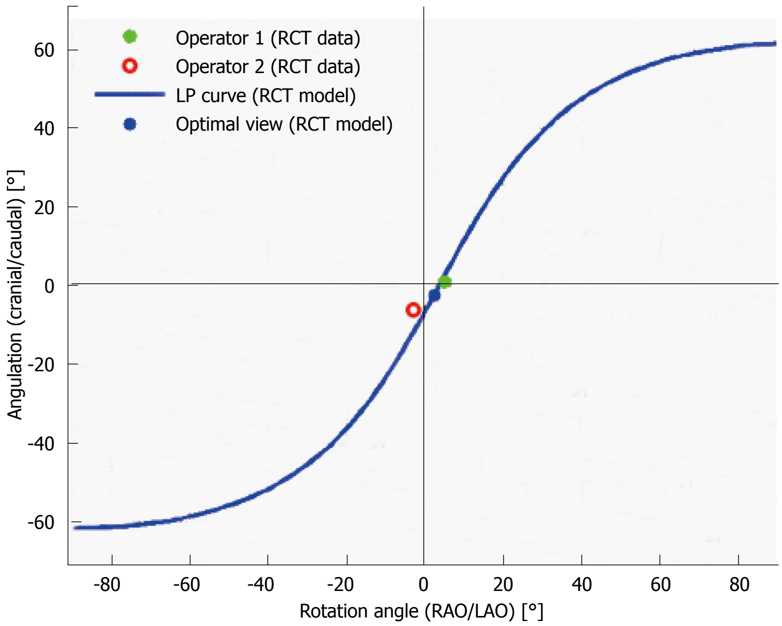

Figure 4 Line of perpendicularity curve for the aortic valve annulus of a sample patient. The solid line represents the line of perpendicularity curve derived from the RCT model; optimal views following the right-cusp rule are given for two operators and the RCT model. RCT: Rotational C-arm computed tomography.

Table 1 Operator variability and model-operator agreement of rotational C-arm computed tomography-based view planning data

n = 57	Average AD (ND)	Average AD (MC)
Operator 1 *vs* operator 2	7.05° ± 3.06°	12.96°
RCT model *vs* both operators	6.84° ± 3.78°	13.82°
RCT model *vs* operator 1	7.14° ± 4.12°	14.37°

To measure the error between two sample C-arm views the angular deviations (AD) are computed and evaluated assuming normal distribution (ND) of the samples and using Monte Carlo (MC) methods. RCT: Rotational C-arm computed tomography.

Massachusetts, United States).

RESULTS

Model-based view planning in RCT

For optimal view planning 57 patients with RCT were evaluated. To assess the inter-observer variability the angular deviations between two expert-defined views in the RCT patient cohort were computed. Assuming normal distribution of the angular deviations, the inter-observer variability was measured to be 7.05° ± 3.06° and thus, in the same range as reported in the work of Tzikas *et al*[8]. Using Monte Carlo methods an interobserver variability between 0° and 12.96° was obtained (compare Table 1 and Figure 3). Furthermore we compared the view planning results of our prototype software with the expert definitions. The model-operator agreement jointly computed for both operators was 6.84° ± 3.78° assuming normal distribution and 0°-13.82° for the Monte Carlo method and thus, on a similar level as the inter-observer variability. A sample LP curve and the respective optimal views of two operators and the prototype software are given in Figure 4.

Model-based intervention guidance

To evaluate the accuracy of RCT-based overlays to interventional data, the dimension of the aortic root at the level of the aortic annulus, the sinus and the

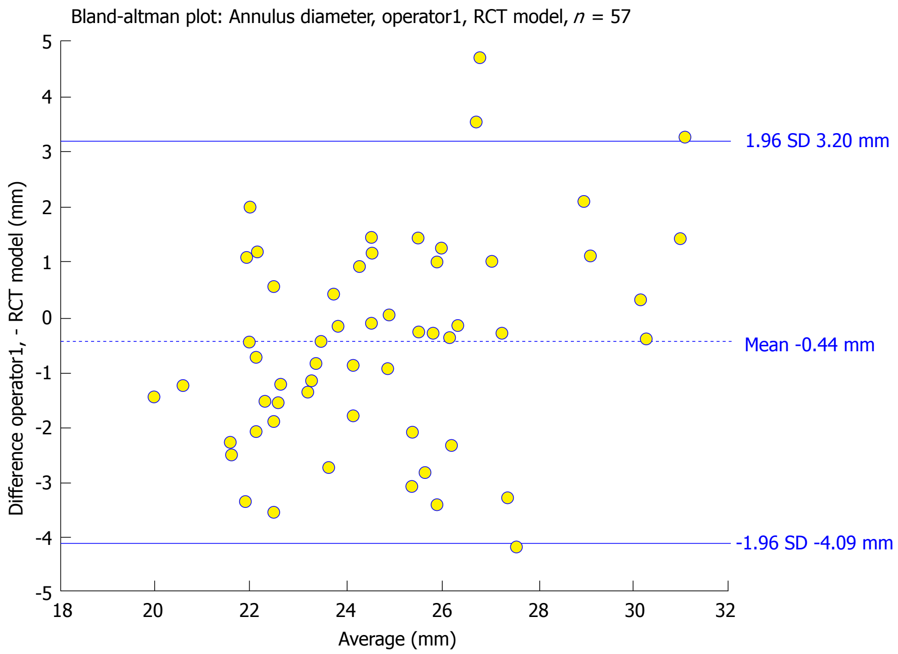

Figure 5 Bland-Altman plot relating aortic annulus diameter measurements done by a medical expert to rotational C-arm computed tomography-model-based measurements. RCT: Rotational C-arm computed tomography.

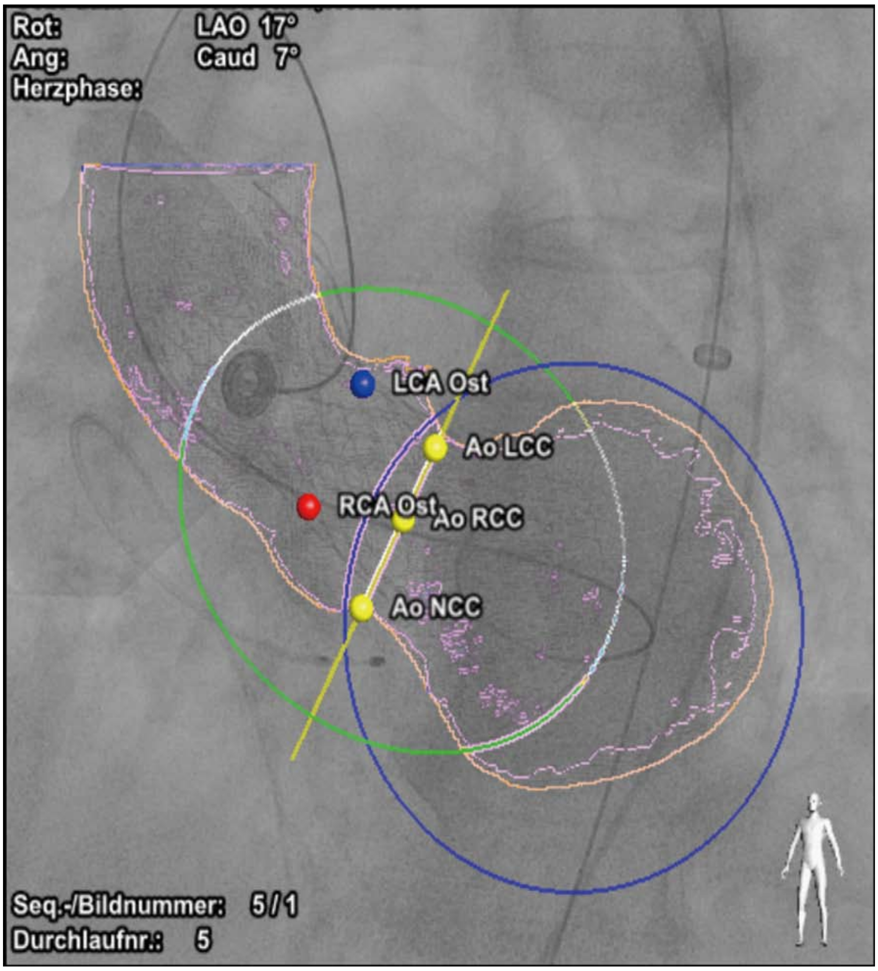

Figure 6 Model-based view planning and interventional overlay with Philips HeartNavigator software.

Table 2 Model-operator agreement for rotational C-arm computed tomography-based diameter measurements

n = 57	Annulus			Sinus			STJ		
	Bias	LoA	*r*	Bias	LoA	*r*	Bias	LoA	*r*
Operator *vs* operator 1	0.32	-3.17-3.81	0.81	-0.45	-3.61-2.71	0.91	-0.59	-3.29-2.10	0.92
RCT model *vs* operator 1	-0.44	-4.09-3.20	0.79	1.05	-1.64-3.75	0.93	-1.53	-4.21-1.15	0.92
RCT model *vs* operator 2	-0.76	-3.75-2.23	0.81	1.51	-0.61-3.62	0.96	-0.94	-3.41-1.53	0.93

To assess bias and deviation of measurements the Bland-Altman analysis is used; in addition the Pearson correlation coefficient is computed to evaluate the inter-measurement agreement considering a significance level of $P < 0.01$. RCT: Rotational C-arm computed tomography; LoA: Limits of agreement (Bland-Altman analysis).

STJ was studied. For all 57 patients in the RCT cohort diameter measurements were obtained from two independent operators and were compared to the model-based measurements. For the aortic annulus the Bland-Altman analysis showed no trend for under- or over-estimation comparing the model-based segmentation results with the expert measurements (mean difference for model *vs* operator 1: -0.44 mm, LoA: -4.09 mm to 3.2 mm). The correlation was significant (r = 0.79). A sample Bland-Altman plot is given in Figure 5. For the aortic sinus width and STJ diameter measurements the scatter and the limits of agreement were slightly smaller and the correlation levels higher as listed in Table 2. The Bland-Altman analysis for the aortic sinus diameter shows a good agreement between model-based and medical expert measurements with a bias of 1.05 mm using RCT and limits of agreement that range from -1.64 mm to 3.75 mm for operator 1. Correlations between expert and model-based measurements varied between 0.93 and 0.96. The results of the STJ diameter measurements show a slight bias of -1.53 mm and the limits of agreement were -4.21 mm to 1.15 mm for operator 1. Model-based and expert measurements correlated on a high level (operator 1: r = 0.92; operator 2: r = 0.93). The interobserver measurements did not show a significant bias. Scatter and correlation levels were for all studied parameters in the same range as the model-operator measurements.

DISCUSSION

Model-based view planning in RCT

Different imaging techniques have been established to define the optimal fluoroscopic view and to optimize valve deployment during TAVR. Standard to define a perpendicular view of the aortic valve is the repeated acquisition of aortographies from different projection angles. During recent years several software solutions for automatic view planning mainly on the basis of MSCT have been developed and have demonstrated high accuracy and many clinical benefits[5].

However, the collection of a MSCT data set for TAVR view planning involves extra logistics for the clinic and additional burden and hazards for the patient. Rotational C-arm CT has proven to be a useful imaging technique for many clinical applications[21] but is less established in the context of TAVR. The image quality of C-arm CT is generally limited by the acquisition quality and thus model-based view planning are dependent on accurate contrast agent bolus timing and on sufficient rapid pacing protocols. According to our clinical experience we believe that with more widespread use and maturity in future, rotational C-arm based imaging can play a more significant role in the TAVR workflow in combination with software-based view planning support.

In this study we evaluated the accuracy of automated view planning with RCT. We could show that our novel prototype software estimates optimal views on the basis of RCT data with good accuracy and that the interobserver variability and model-operator agreement are in the same range. Although different contrast agent injection protocols (aortic root injection *vs* left-ventricular injection) were part of the RCT validation cohort the model-based view planning in RCT has proven to be robust.

RCT-based intervention guidance

The current standard for intervention guidance during TAVR is plain fluoroscopy. In recent years software such as the HeartNavigator software (Philips Healthcare, Andover, MA, United States; compare Figure 6) that segments a three-dimensional MSCT data set to create a patient-specific model of the heart and overlays this to the interventional image stream has been developed. In this study we examined the accuracy of RCT-based overlays that are automatically generated from model-based segmentation. We found that our RCT-based techniques are able to accurately reflect the dimension of the aortic valve annulus and the aortic root. Bias and variations of model-based measurements *vs* the experts' references were in the same range as the operator variability. Thus, RCT modeling can potentially provide accurate anatomical overlays to interventional data to support the TAVR intervention as current software solutions already do for MSCT.

In conclusion, established and upcoming complex cardiac interventions such as TAVR require detailed information regarding heart and vessel anatomy for procedure planning and intra-procedural guidance. According to our experience, rotational C-arm CT can be smoothly integrated into the clinical workflow, providing three-dimensional information of the relevant anatomical structures in the catheterization lab prior and as part of the TAVR intervention.

Limitations

This study was based on retrospective data and reflects solely the experience at our center. The RCT data was acquired during TAVR/SAVR procedure planning several days in advance to the procedure. The data in this study were based on a relatively small sample size to show the clinical feasibility. Possible clinical benefits have to be investigated in prospective studies with more standardized protocols and a more powerful sample size. Future studies should prove feasibility and accuracy of RCT acquisition as initial step during TAVR procedure which may increase accuracy of view planning and intervention guidance further due to fewer patient position changes. In addition, RCT-based calcium visualization and quantification has to be studied.

COMMENTS

Background

Optimal positioning of the prosthetic valve is crucial for procedural success of Transcatheter aortic valve replacement (TAVR). Optimal and safe device deployment is best accomplished by generating a specific fluoroscopic view perpendicular to the annulus plane, also known as the line of perpendicularity (LP). To achieve this specific fluoroscopic view during the TAVR procedure, several angiograms in different angulations of the C-arm are necessary, causing a considerable amount of nephrotoxic contrast agent and radiation for the patient and the operator. Different imaging techniques have been established to define the LP optimal fluoroscopic view during the preprocedural screening of patients. Multi-slice computed tomography (MSCT) is the preferred modality and "gold-standard" for TAVR planning and intervention guidance. For angiography and MSCT different software solutions for optimal view planning and their clinical benefits have been proposed. Automated view planning along the LP has shown to improve the quality of implantation, may speed up workflow and may reduce the need for low-dose aortograms. Rotational C-arm CT (RCT)-based view planning has proven to be of equal quality as MSCT-based techniques.

Research frontiers

Current studies purely rely on non-quantitative evaluations and a systematic validation of software-based methods is lacking. RCT has proven to be a useful imaging technique for many clinical applications but is less established in the context of TAVR. According to the achieved clinical experience a more widespread use of RCT-based imaging could play a more significant role in the TAVR workflow in combination with software-based view planning support in the future.

Innovations and breakthroughs

This study is the first which combines the evaluation concerning the accuracy of a RCT- based 3D heart model for segmentation of the aortic root and prediction of the LP and its suitability for intervention guidance. The authors could show that their novel prototype software estimates optimal views on the basis of RCT data and that the model-based view planning in RCT has proven to be robust.

Applications

According to the authors' results, RCT can be smoothly integrated into the clinical workflow, providing three-dimensional information of the relevant anatomical structures in the catheterization lab prior and as part of the TAVR intervention.

Terminology

RCT is an imaging diagnostic tool to predict an optimal C-arm configuration during TAVR. RCT was performed as part of the pre-implant diagnostic coronary angiography study. To mitigate motion the acquisition was conducted during inspiratory breath hold and under rapid ventricular pacing. With prototype software each RCT data set was segmented using a 3D heart model. From that the LP curve was obtained that generates a perpendicular view of the aortic annulus according to the right-cusp rule. To evaluate the accuracy of a model-based overlay we compared model- and expert-derived aortic root diameters.

Peer-review

The authors are congratulated with their meticulous work on the use of rotational C-arm 3D heart model for prediction of an optimal C-arm configuration to be used before and during the procedure of transcatheter aortic valve replacement.

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P- Reviewer: Farand P, Said SAM, Tagarakis G **S- Editor**: Qiu S **L- Editor**: A **E- Editor**: Wu HL

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DOI: 10.4330/wjc.v8.i10.615

World J Cardiol 2016 October 26; 8(10): 615-622
ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Randomized Controlled Trial

Randomized controlled trial of remote ischemic preconditioning and atrial fibrillation in patients undergoing cardiac surgery

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Institutional review board statement: The study was reviewed and approved by the Institutional Review Board of Baystate Medical Center.

Clinical trial registration statement: The study was registered at http://www.clinicaltrials.gov prior to study enrollment (Identifier NCT01500369).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All authors declare no potential conflicting interests related to this paper.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

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Received: April 25, 2016
Peer-review started: April 26, 2016
First decision: May 17, 2016
Revised: August 5, 2016
Accepted: August 27, 2016
Article in press: August 29, 2016
Published online: October 26, 2016

Abstract

AIM
To study whether remote ischemic preconditioning (RIPC) has an impact on clinical outcomes, such as post-operative atrial fibrillation (POAF).

METHODS
This was a prospective, single-center, single-blinded,

randomized controlled study. One hundred and two patients were randomized to receive RIPC (3 cycles of 5 min ischemia and 5 min reperfusion in the upper arm after induction of anesthesia) or no RIPC (control). Primary outcome was POAF lasting for five minutes or longer during the first seven days after surgery. Secondary outcomes included length of hospital stay, incidence of inpatient mortality, myocardial infarction, and stroke.

RESULTS

POAF occurred at a rate of 54% in the RIPC group and 41.2% in the control group (P = 0.23). No statistically significant differences were noted in secondary outcomes between the two groups.

CONCLUSION

This is the first study in the United States to suggest that RIPC does not reduce POAF in patients with elective or urgent cardiac surgery. There were no differences in adverse effects in either group. Further studies are required to assess the relationship between RIPC and POAF.

Key words: Chronic ischemic heart disease; Cardiac surgery; Coronary artery disease; Other treatment; Remote ischemic preconditioning; Post-operative atrial fibrillation

Core tip: This is the first study in the United States to suggest that remote ischemic preconditioning does not reduce post-operative atrial fibrillation in patients with elective or urgent cardiac surgery.

Lotfi AS, Eftekhari H, Atreya AR, Kashikar A, Sivalingam SK, Giannoni M, Visintainer P, Engelman D. Randomized controlled trial of remote ischemic preconditioning and atrial fibrillation in patients undergoing cardiac surgery. *World J Cardiol* 2016; 8(10): 615-622 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i10/615.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i10.615

INTRODUCTION

Post-operative atrial fibrillation (POAF) is the most common arrhythmia after coronary artery bypass grafting (CABG)[1]. Despite improvement in medical therapy, surgical technique, and anesthesia, POAF occurs in 25%-40% of patients undergoing CABG and valve surgery[1-4]. POAF remains challenging to prevent, treat, or cure[5], and contributes to increased short and long term mortality[6,7], stroke[8], an increase in length of hospital stay[9], intensive care unit readmission, and treatment costs[10]. Some factors associated with POAF include a patient's preoperative status, age, and preexisting electrocardiogram abnormalities[11]. Intra-operative stress also plays a key role, due to occurrence of reperfusion, inflammation, oxidative stress, and/or hemostasis[12-14]. Most POAF episodes occur within the first 6 d following cardiac surgery, with the peak incidence on the second or third post-operative day, coinciding with the peak of systemic inflammation caused by surgery and with atrial stretch[8].

Remote ischemic preconditioning (RIPC) is one strategy that has shown a myocardial protective effect during CABG and heart valve surgery[15-17]. It was first described in 1986 in a dog model, where RIPC provided a protective effect on the myocardium that was later subjected to a sustained bout of ischemia[18]. RIPC was shown to reduce the incidence of ischemic reperfusion ventricular arrhythmias[19]. There is evidence that RIPC can preserve mitochondrial function and influences myocardial microRNA expression of the right atrium, potentially decreasing the incidence POAF after CABG surgery[20,21]. In addition, the efficacy of preconditioning to reduce myocardial injury in cardiac surgery and percutaneous coronary interventions has also been demonstrated[22].

There is growing evidence that AF is associated with increased inflammation[23,24], and Jannati *et al*[25], demonstrated that myocardial ischemic preconditioning by aortic cross-clamping in patients undergoing CABG reduced the incidence of POAF.

Currently, there is no optimal preconditioning protocol or tool being utilized during cardiac surgery and aortic cross-clamping may increase the risk of embolic stroke, particularly in elderly patients[26]. We conducted a randomized clinical trial to assess if RIPC can reduce POAF after CABG, with or without concomitant valve surgery or valve surgery alone.

MATERIALS AND METHODS

Study design

This study was a prospective, single-center, single-blinded, randomized controlled trial. The trial was registered with www.clinicaltrials.gov (NCT01500369).

Patient population

Patients who were undergoing non-emergent cardiac surgery were screened and recruited from the cardiac surgical service.

Eligibility

Eligible patients were adults greater than 18 years old who were referred for elective or urgent CABG, with or without valve surgery, or valve surgery alone between April 2011 and October 2013.

Exclusion criteria included any preoperative rhythm detected other than a sinus rhythm, a history of AF, New York Heart Association Ⅳ congestive heart failure, cardiogenic shock, emergent CABG and/or valve surgery, bleeding diathesis, patients taking K(+) ATPase channel blockers (sulphonylureas), and women of childbearing age. Patients were contacted by the primary investigator or a cardiology fellow to explain the study and obtain consent. This occurred during the 24-h period after undergoing cardiac catheterization (urgent care patients) or during a pre-op office visit (elective surgery patients). Patients who were interested gave written informed consent. Trial approval was obtained from the Institutional Review Board and the study is registered at http://www.clinicaltrials.gov; identifier NCT01500369. Upon consent, participants were randomized during the pre-operative period to either the treatment or control group.

Blinding

Patient blinding: Patients were randomly assigned to a treatment strategy (RIPC/no RIPC) in the operative room during the 45-min pre-operation period. Randomization occurred after patients were anesthetized; thus, patients were unaware of their treatment assignment.

Physician blinding: Since randomization and the RIPC procedure were conducted preoperatively, we expect that the surgeons were unaware of patient treatment assignment, and an effort was made to prevent surgeon knowledge of which group was selected.

Randomization process

The randomization schedule was developed by the institution’s statistical core facility and patients were randomized according to a computer-generated randomization procedure. Patients were randomized using blocks in sizes 4 and 6, administered in a random fashion.

Consecutively-numbered envelopes were created and populated with a patient identification and the treatment assignment, based on the random block. The envelopes were kept in a locked cabinet. When an eligible patient was identified, consented, and moved to the pre-operative area, the staff member would select the next envelope in the consecutive list and give it to the research nurse. The research nurse would open the envelope and proceed as indicated on the enclosed form.

Study procedures

For all study participants, anesthesia was induced with intravenous propofol (0.5-2 mg/kg), midazolam (0.04-0.05 mg/kg), fentanyl (1-5 μg/kg), and rocuronium (0.6-1 mg/kg), and maintained with isoflurane. On-pump surgical revascularization was achieved through a median sternotomy. The internal thoracic arteries, radial arteries, and saphenous veins were used as grafts. Heparin was administered to achieve an activated clotting time longer than 400 s. Standard non-pulsatile cardiopulmonary bypass with a membrane oxygenator was used with an ascending-aortic and two-stage venous cannulation. During cardiopulmonary bypass, moderate hemodilution with a hematocrit of approximately 25% and mild systemic hypothermia (32 ℃) were maintained. Retrograde warm blood cardioplegia was used for all distal anastomoses. Proximal anastomoses were constructed with partial side clamping of the ascending aorta. Bypass graft flow was assessed with an ultrasonic transit time-flow measurement probe. After reperfusion and weaning from cardiopulmonary bypass, protamine was administered for heparin reversal. For hemodynamic support, inotropes and/or vasopressors were infused as required.

RIPC, for those in the study arm, took place after induction of anesthesia and prior to skin incision during which time the patient was prepped, draped, and prepared for surgery using the following protocol.

Treatment group: Patients in the treatment group received 3 sequential sphygmomanometer cuff inflations on their right upper arm after induction of anesthesia in the operating room. The cuff was inflated to 200 mmHg for five minutes each occasion, with a period of five minutes deflation between inflations. The entire RIPC phase lasted 30 min.

Control group: Patients in the control group had the sphygmomanometer cuff placed on their right upper arm, but the cuff was not inflated. Similar to patients in the treatment group, patients in the control group had to undergo the same 30 min delay before the initiation of a skin incision.

Outcome events

Primary outcome: The primary outcome was POAF lasting for five minutes or longer during the first seven days after surgery. This outcome was assessed by using patient’s hospital records as well as the Society of Thoracic Surgery (STS) database which records outcomes up until 30 d after surgery.

Secondary outcomes: Secondary outcomes such as length of hospital stay, inpatient death, myocardial infarction (MI), and stroke were recorded during the study follow-up period. Additionally, using the STS definitions for perioperative outcomes (Table 1), the 30-d death, MI, stroke, and readmission were obtained from the institutional STS database.

Adverse outcomes: Adverse events were documented after the initiation of the protocol.

Statistical analysis

Treatment and control groups were compared on baseline characteristics to identify whether randomization was successful. Continuous variables were compared using 2-sample t tests or the non-parametric equivalent (Wilcoxon rank-sum test), while categorical variables were compared using Pearson χ^2 or Fisher’s exact test. For dichotomous outcomes, logistic regression was used to adjust for group imbalances, when necessary. To examine whether treatment assignment influenced

Table 1 Society of thoracic surgery definitions for peri-operative outcomes

Outcomes	Definition
Stroke	If the patient had a central neurological deficit persisting postoperatively for > 72 h
Peri-operative MI	0-24 h post-operative: The CK-MB (or CK if MB not available) must be greater than or equal to 5 times the upper limit of normal, with or without new Q waves present in two or more contiguous ECG leads No symptoms required > 24 h post-operative: Indicate the presence of a peri-operative MI (> 24 h post-op) as documented by at least one of the following criteria: (1) Evolutionary ST-segment elevations (2) Development of new Q-waves in two or more contiguous ECG leads (3) New or presumably new LBBB pattern on the ECG (4) The CK-MB (or CK if MB not available) must be greater than or equal to 3 times the upper limit of normal

MI: Myocardial infarction; ECG: Electrocardiogram.

Table 2 Baseline characteristics between control group and remote ischemic preconditioning group

Characteristic	Control (*n* = 51)	RIPC (*n* = 51)	*P*
Demographics			
Mean age (± SD)	68.9 (± 9.8)	69.4 (± 9.9)	0.77
Male % (*n*)	62.8 (32)	76.5 (39)	0.20
Caucasian % (*n*)	88.2 (45)	90.2 (46)	1.00
Mean BMI (± SD)	30.4 (± 7.6)	28.4 (± 5.2)	0.13
Co-morbidities			
Diabetes mellitus % (*n*)	39.2 (20)	62.7 (32)	0.029
Hypertension % (*n*)	84.3 (43)	82.4 (42)	1.00
Dyslipidemia % (*n*)	90.2 (46)	90.2 (46)	1.00
Heart failure % (*n*)	21.6 (11)	23.5 (12)	1.00
Atrial fibrillation % (*n*)	0.0 (0)	0.0 (0)	NA
AICD % (*n*)	0.0 (0)	2.0 (1)	1.00
CVA % (*n*)	3.9 (2)	5.9 (3)	1.00
TIA % (*n*)	2.0 (1)	7.8 (4)	0.36
PAD % (*n*)	9.8 (5)	21.6 (11)	0.17
CKD % (*n*)	23.5 (12)	23.5 (12)	1.00
Dialysis % (*n*)	2.0 (1)	2.0 (1)	1.00
Mean creatinine (± SD)	1.2 (± 1.1)	1.2 (± 0.7)	0.89
COPD % (*n*)	5.9 (3)	0.0 (0)	0.24
Tobacco use % (*n*)	17.6 (9)	27.5 (14)	0.34

AICD: Automatic implantable cardioverter-defibrillator; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; CVA: Cerebrovascular accident; TIA: Transient ischemic attack; PAD: Peripheral arterial disease; RIPC: Remote ischemic preconditioning.

time to first occurrence of POAF, a log-rank test of the Kaplan-Meier survival functions was conducted.

RESULTS

A total of 102 patients were randomized between April 2011 and September 2013 (Figure 1). Sixty-nine point nine percent of the patients were males and 89% were Caucasian (Table 2). The mean age of patients in the RIPC and control group was 69.4 and 68.9 years, respectively. With the exception of diabetes mellitus, the two groups were balanced with respect to baseline characteristics. Study groups were also well balanced with respect to medication use including beta blocker and HMG-CoA reductase inhibitors (statins). 46% of the patients presented with acute coronary syndrome and 23.5% presented with stable angina and were well matched (Table 3).

POAF occurred at the rate of 54.0% in the RIPC group and 41.2% in the control group (P = 0.23). Expressed as a difference in proportions, the percent of patients experiencing POAF was 12.8% higher in the RIPC group compared with the usual care group (95%CI: -6.5%-32.1%). Although the presence of diabetes was significantly higher in the RIPC group, it was not associated with any outcome, and consequently, adjusting for diabetes in logistic regression models did not materially change the univariable results.

No post-operative MIs occurred in the RIPC group while 3.9% did in the control group, although this difference was not statistically significant (P = 0.50) (Table 4). There were only two deaths and two strokes for the entire study group and both occurred in the RIPC group. The 30-d readmission rates demonstrated no statistically significant difference between the two groups. The length of stay, left ventricular ejection fraction, and cross-clamp time demonstrated no significant difference between the control and RIPC groups.

The event rate for POAF, based on Kaplan-Meier analysis, was not significantly different between the RIPC and control group (P = 0.13) (Figure 2). No adverse events related to RIPC occurred.

DISCUSSION

In our study that assessed the effect of RIPC on clinical outcomes in patients undergoing elective or urgent cardiac surgery, we found that RIPC did not reduce POAF. In addition, there were no statistically significant differences in secondary outcomes, including post-operative MI and stroke and no adverse events were reported with RIPC.

The Effect of Remote Ischemic Preconditioning on Clinical Outcomes in CABG Surgery (ERICCA) study randomized 1216 patients who underwent CABG to RIPC *vs* control and demonstrated that at one year there was no statistically significant difference in the primary clinical outcome (cardiovascular clinical death, MI, stroke and coronary revascularization)[27]; no data regarding POAF were provided. Previous studies to date have largely evaluated the impact of RIPC on surrogate markers of clinical outcomes. RIPC has been evaluated in patients undergoing percutaneous coronary intervention to reduce myocardial injury[28], reduce contrast-induced nephropathy[29], and myocardial salvage in

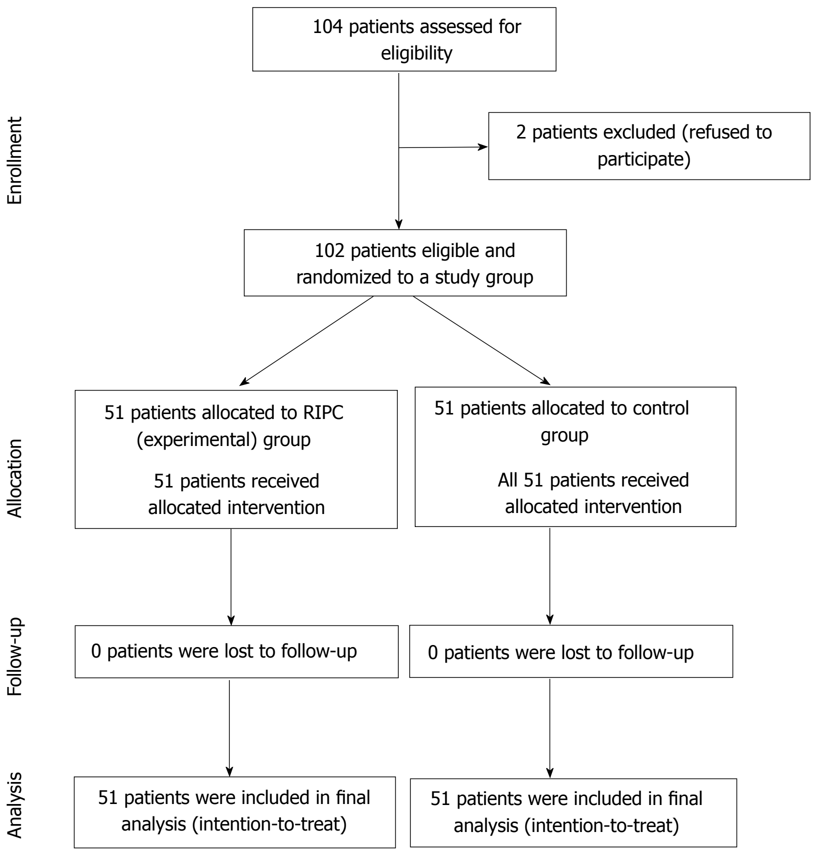

Figure 1 Randomization and follow up of patients. RIPC: Remote ischemic preconditioning.

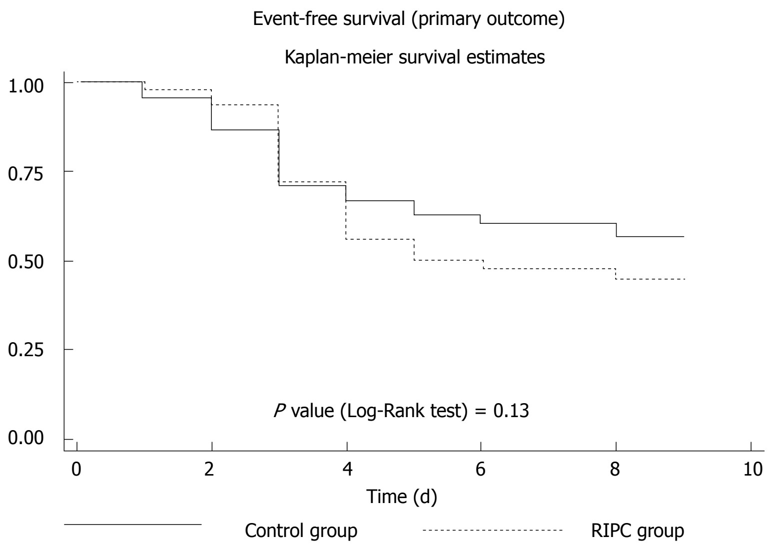

Figure 2 Kaplan-Meier estimates of the probability of remaining free from post-operative atrial fibrillation, according to study group. RIPC: Remote ischemic preconditioning.

ST-segment elevation MI[30]. Specifically, in patients undergoing cardiac surgery, RIPC has been known to decrease myocardial injury measured by cardiac troponin release[31,32]. At the same time, several other trials have failed to show improvement in surrogate outcomes with the implementation of RIPC[33,34], and this can be attributed to variable protocols, medications, surgical, and anesthetic regimens. It is also difficult to draw any conclusions regarding clinical outcomes from these studies as they were included only as secondary outcomes, often under-powered and had varying definitions of clinical outcomes[35]. Thus, no trials have been published demonstrating that RIPC significantly reduced clinical endpoints in patients undergoing cardiac surgery[36].

The rate of POAF in our study was higher than

Table 3 Baseline medications and clinical presentation in the control group and remote ischemic preconditioning group

Characteristic	Control (*n* = 51)	RIPC (*n* = 51)	*P*
Medications % (*n*)			
Alpha blockers	7.8 (4)	2.0 (1)	0.36
Beta blockers	78.4 (40)	80.4 (41)	1.00
ACE-inhibitors	37.3 (19)	41.2 (21)	0.84
Aspirin	90.2 (46)	90.2 (46)	1.00
Statins	84.3 (43)	86.3 (44)	1.00
Clinical presentation % (*n*)			
Stable angina	23.5 (12)	23.5 (12)	1.00
Unstable angina	25.5 (13)	25.5 (13)	1.00
Positive stress test	27.5 (14)	25.5 (13)	1.00
Non-STEMI	19.6 (10)	17.6 (9)	1.00
STEMI	0.0 (0)	2.0 (1)	1.00
Valve without CAD	17.6 (9)	27.5 (14)	0.34

ACE: Angiotensin converting enzyme; CAD: Coronary artery disease; RIPC: Remote ischemic preconditioning; STEMI: ST-elevation myocardial infarction.

Table 4 Clinical outcomes in the control group *vs* remote ischemic preconditioning group

Characteristic	Control (*n* = 51)	RIPC (*n* = 51)	*P*
Primary endpoint			
POAF % (*n*)	41.2 (21)	54.0 (27)	0.23
Secondary endpoints			
Other arrhythmia % (*n*)	13.7 (7)	11.8 (6)	1.00
MI % (*n*)	3.9 (2)	0.0 (0)	0.50
Stroke % (*n*)	0.0 (0)	3.9 (2)	0.24
Mean EF (± SD)	53.1 (± 14.8)	50.5 (± 16.9)	0.43
Bleeding % (*n*)	21.6 (11)	28.0 (14)	0.50
Mean cross-clamp time (± SD)	88.7 (± 44.8)	93.0 (± 38.5)	0.61
In-hospital mortality % (*n*)	0 (0)	3.9 (2)	0.50
30-d mortality (after discharge) % (*n*)	0 (0)	0 (0)	1.0
30-d readmission % (*n*)	11.8 (6)	16.3 (8)	0.57
Mean LOS (± SD)	13.7 (± 7.8)	14.0 (± 7.7)	0.87

EF: Ejection fraction; LOS: Length of stay; MI: Myocardial infarction; POAF: Post-operative atrial fibrillation; RIPC: Remote ischemic preconditioning; STEMI: ST-elevation myocardial infarction.

expected in both groups, which could be related to the small sample size and the presenting co-morbidities. Additionally, the absolute numbers of secondary outcomes recorded were quite small and therefore, are only exploratory at this stage. The unreliability of studies with small study samples is well-known[37,38]. Even if significant results had emerged from our study, regardless of direction of effect, we would caution against the over-interpretation of results, since small studies often produce large effects that frequently defy replication[39]. To our knowledge, this is the first study undertaken in the United States to assess the relationship of RIPC with POAF. Although this small study found no significant association of RIPC with clinical outcomes, it serves as an addition to the sparse literature on RIPC and clinical outcomes and would be of value when additional small studies are published. Meta-analyses of randomized controlled studies could yield a more accurate estimation of the true relationship between RIPC and POAF by combining patients and increasing sample power.

There were several limitations to our study that may have contributed to it not resulting in a positive finding. First, the study was halted prematurely, due to the lack of financial support to continue recruitment, which led to a study with less power than intended. However, given a control POAF rate of 50% (as seen in this population), the study still had 70% power to detect a 25% percentage points difference. Second, there was a significantly higher percentage of patients with diabetes mellitus in the RIPC arm, which may have masked the beneficial effect of RIPC[40]. However, this is unlikely to have significantly confounded the results as there was no change in the relationship of RIPC with outcomes even after adjustment using logistic regression analysis. Third, there is some recent evidence that patients given propofol may not gain protection from RIPC[41,42], possibly related to its structure being similar to that of phenol-based radical scavengers. This study was started prior to the publication of the study by Kottenberg *et al*[41], and in our study, propofol was used for the induction of anesthesia, not for maintenance. As with the majority of RIPC studies[35], we performed 3 cycles of RIPC, and in future trials it may be necessary to perform more than 3 cycles of blood pressure cuff inflation to provide clinical benefit. A final limitation is that warm cardioplegia has demonstrated a reduction in myocardial injury as compared to cold cardioplegia with similar clinical events[43,44]. Given that all our patients received warm cardioplegia, this could have masked the benefit of RIPC.

Despite the fact that the results of this study suggest that there is no beneficial effect of RIPC on reducing POAF, RIPC still holds promise in improving clinical outcomes, based on "proof-of-concept" studies using cardiac biomarkers as primary endpoints[31,45,46] and, due to the fact it is a simple, safe, non-invasive, and inexpensive intervention. Although it has been challenging to identify which groups of patients benefit from RIPC, further evaluation of RIPC to decrease post-operative events with carefully planned and funded studies with adequate power is warranted. Additionally, meta-analysis of small randomized controlled studies may also be useful in studying the relationship of RIPC and clinical outcomes, including POAF.

COMMENTS

Background

Remote ischemic preconditioning (RIPC) has been demonstrated to reduce perioperative myocardial injury following cardiac surgery (coronary artery bypass, with or without valve surgery).

Research frontiers

It is unknown whether it has an impact on clinical outcomes, such as post-operative atrial fibrillation, peri-operative myocardial infarction and stroke.

Innovations and breakthroughs

This is the first study in the United States evaluating these clinical outcomes following the use of RIPC with cardiac surgery.

Applications

Although this study did not suggest a clinically significant benefit with the use of RIPC, future meta-analyses of small randomized controlled studies may be useful in studying its relationship with clinical outcomes.

Terminology

RIPC is a strategy in which brief episodes of non-lethal ischemia and reperfusion are applied to the arm or leg in order to achieve myocardial protection from ischemic events.

Peer-review

This is an interesting manuscript about the effect of (PIPC on clinical outcomes such as post-operative atrial fibrillation (POAF), myocardial infarction, stroke, and mortality in 102 patients undergoing cardiac surgery. The data demonstrated that PIPC did not reduce POAF. In addition, there were no significant differences in post-operative myocardial infarction, stroke, and mortality between RIPC group and control group. Therefore, the authors have suggested that further evaluations of RIPC are required to decrease post-operative events.

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P- Reviewer: Chu D, Firstenberg MS, Kettering K, Ueda H
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Wu HL

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