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RATIONALE AND DESIGN OF SCREENING OF PULMONARY HYPERTENSION IN METHAMPHETAMINE ABUSERS (SOPHMA) STUDY

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Keywords:	methamphetamine, pulmonary hypertension, screening

RATIONALE AND DESIGN OF A SCREENING OF PULMONARY HYPERTENSION IN METHAMPHETAMINE ABUSERS (SOPHMA) STUDY

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ABSTRACT

Introduction: Methamphetamine misuse is classified as a ‘‘likely’’ risk factor for pulmonary arterial hypertension (PAH). Nevertheless the actual prevalence of and a screening strategy for PAH in methamphetamine users have not been established. We plan to study the prevalence of PAH and identify its independent risk factors among methamphetamine users.

Methods and analysis: This will be a multi-center, cross-sectional screening study that will involve substance abuse clinics in Hong Kong that cater to more than 20 methamphetamine users. A total of 200 patients who (1) are ≥18 years at enrolment; (2) report methamphetamine use in the last 2 years; (3) are diagnosed as amphetamine dependent; and (3) voluntarily agree to participate by providing written informed consent will be included. Patients will undergo standard echocardiography-based PAH screening procedures recommended for those with systemic sclerosis. Right heart catheterization will be offered to participants with a high echocardiographic probability of PAH. For participants with a low or intermediate echocardiographic probability of PAH, rescreening will be performed within 1 year. The primary measure will be the diagnosis and subtypes, as well as prevalence of PAH in methamphetamine users. The secondary measures will be the risk factors and a prediction model for PAH in methamphetamine users.

Ethics and dissemination: The SOPHMA study has been approved by the institutional review board. Our results will determine the prevalence and the types of PAH, and identify individual risk factors for its development in methamphetamine users. Ultimately this study will provide the necessary evidence to establish universal guidelines for screening of PAH in methamphetamine users.

Keywords: methamphetamine, pulmonary hypertension, screening

STRENGTH AND LIMITATIONS

1. The SOPHMA study will be the first to evaluate the prevalence of and identify risk factors for PAH among methamphetamine users.
2. This study will apply a current guideline-recommended PAH screening algorithm for systemic sclerosis to unselected methamphetamine users.
3. The screening strategy is an echocardiography-based protocol. Right heart catheterization will be confined to those with a high echocardiographic probability of PAH in accordance with guideline recommendations.
4. The restricted application of right heart catheterization to those with high echocardiographic probability of PAH may under-estimate the "true" prevalence of PAH in methamphetamine users.

INTRODUCTION

Methamphetamine is a potent central nervous system stimulant originally prescribed for individuals with a neuropsychiatric disorder such as attention-deficit hyperactivity disorder. Due to its highly addictive nature, illicit methamphetamine use is emerging as a major public health problem worldwide. In 2013 the United Nations Office on Drugs and Crime reported that 0.7% of the global population aged between 15 and 64 years, i.e., 33.8 million individuals, reported use of methamphetamine and/or related compounds in 2010.[1] This illicit methamphetamine use is expected to increase.[1] In addition to the infamous methamphetamine use disorder, which is primarily a psychiatric condition due to the neurocognitive effects of methamphetamine,[2] methamphetamine also affects the cardiovascular system. Chronic sympathetic activation leads to hypertension, cardiac arrhythmias, ischemic strokes, and myocardial infarction. As methamphetamine can be inhaled in a vaporized form and smoked or snorted, serious respiratory complications can also ensue including pulmonary arterial hypertension (PAH).

PAH is a devastating and often life-threatening condition. It is hemodynamically defined as an elevated mean pulmonary artery pressure ≥25 mmHg and elevated pulmonary vascular resistance ≥ 3 WU combined with a normal pulmonary artery wedge pressure ≤ 15 mmHg in the absence of significant lung disease and/or chronic thromboembolic pulmonary hypertension. The association of PAH with methamphetamine use was first described in a case report in 1993.[3] In a subsequent retrospective cohort, patients with idiopathic PAH were found to have a much higher prevalence of prior use of methamphetamine and/or its related compounds (28.9%), compared with patients with chronic thromboembolic pulmonary hypertension (4.3%) or pulmonary hypertension due to

a known associated condition (3.8%).[4] Although current international guidelines recognise methamphetamines as a "likely" cause of drug-induced PAH,[5] almost nothing is known about its prevalence and incidence amongst methamphetamine users.

In the REVEAL registry (Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension disease management),[6] a 55-center longitudinal United States-based PAH registry, the estimated 5-year survival from diagnosis of PAH was 49%. Since patients with PAH often remain asymptomatic in the early phase, the diagnosis is often made late in the course of the disease, when most small pulmonary arteries have been obliterated, rendering therapy ineffective.[7] As such, international guidelines recommend routine screening with resting transthoracic echocardiography and biomarkers to promptly detect PAH in asymptomatic high-risk individuals such as those with systemic sclerosis.[5 8] Although the prognosis of patients with methamphetamine-associated PAH appears to be much worse than for those with idiopathic PAH,[9] international guidelines[5] and expert consensus[10] have not considered screening for PAH in asymptomatic methamphetamine users. The lack of a screening effort for PAH amongst methamphetamine users is due to the unknown prevalence of PAH in this population that adversely affects the cost effectiveness of any screening procedure.[8] This hampers the prospect of identifying risk factors of PAH[11] and developing a prediction model for the occurrence of PAH in methamphetamine users.

The **S**creening **O**f **P**ulmonary **H**ypertension in **M**ethamphetamine **A**busers (**SOPHMA**) Study is a cross-sectional screening study that will apply a current guideline-recommended PAH screening

algorithm for systemic sclerosis to a large cohort of unselected methamphetamine users in Hong Kong.[5 12] The study objectives include:

(1) To describe the prevalence of PAH amongst methamphetamine users using a current guideline-recommended screening algorithm for PAH in systemic sclerosis;

(2) To identify independent risk factors for PAH in methamphetamine users; and

(3) To develop a prediction model for PAH in methamphetamine users.

METHODS AND ANALYSIS

Study design

SOPHMA is a multi-center, cross-sectional screening study based in Hong Kong (Figure 1). Participating centres must have a specialized substance abuse clinic with a minimum 20 methamphetamine users actively followed up of whom more than 80% consent to participate in the study.

Patients and Patient Recruitment strategy

Participants who fulfil the following criteria will be invited to participate in the study: (1) age ≥ 18 years at enrolment; (2) report of methamphetamine use in the last 2 years, (3) diagnosed with amphetamine dependence according to the Diagnostic and Statistical Manual of Mental Disorders (the 5th edition)(DSM-V),[13] and (3) voluntary agreement to participate by providing written informed consent. Participants with a history of methamphetamine use followed-up in the participating substance abuse clinic will be identified via the computerized database of the clinical management system and will be contacted by a research nurse. The design and objectives of the study will then be discussed with the research nurse. An invitation information leaflet detailing the study will be provided to the candidate patients at the same time. Patients who fail or refuse to provide written informed consent will be excluded. Table 1 summarizes the five items included in the study screening procedure. According to the guidelines,[5] standard right heart catheterization will be performed in patients with a high echocardiographic probability of pulmonary hypertension. For those with a low or intermediate echocardiographic probability, screening will be repeated within 1 year to ensure true negativity of the original scan.

Demographic and Serum Data Collection

Demographic data and a detailed history of methamphetamine use will be recorded. In addition, cardiovascular risk factors, history of other cardiovascular diseases, investigative results in the last 3 months including NT-proBNP, liver and renal function as well as serum urate will be recorded. Table 2 summarizes the demographic data and other cardiovascular risk factors and/or conditions to be collected.

Echocardiographic examination

Detailed quantitative transthoracic echocardiography examination including two-dimensional, M-mode, and Doppler flow studies will be performed in all patients. Standard two-dimensional and M-mode measurements will be performed according to the recommendations of the American Society of Echocardiography.[14] Valvular regurgitation will be classified as mild, moderate, or severe using a semi-quantitative method.[15] A standard Doppler echocardiographic method will be used to estimate cardiac output.[16] For calculation of cardiac output, an average of five consecutive ventricular systoles during sinus rhythm, or an average of 13 beats in case of atrial fibrillation, will be obtained.[17] Simultaneous blood pressure measurements will be recorded with a calibrated non-invasive semiautomatic device (Dinamap 1846XT; Critikon Corp., Tampa, FL) during the determination of cardiac output. Total vascular resistance (TVR) in dyne-sec/cm^5 will be calculated using the following formula:

$$Total\ Vacsular\ Resistance\ (\text{dyne} - \frac{\text{sec}}{\text{cm5}}) = 80\ x \frac{mean\ arterial\ blood\ pressure\ (mmHg)}{Cardiac\ output\ (L/min)}$$

For the right heart, specific transthoracic echocardiographic measurements will be performed based on the Guidelines for the Echocardiographic Assessment of the Right Heart in Adults from the American Society of Echocardiography that are endorsed by the European Association of

Echocardiography.[18] Specifically, right atrial (RA) dimension will be assessed using RA area (normal <18 cm^2), RA length (normal <53 mm) and RA diameter (normal <44mm). Right ventricular (RV) dimension will be estimated at the base (normal: <42 mm) and at the mid-level (normal: <35 mm) as well as the longitudinal dimension (normal: <86 mm) at end-diastole from a RV-focused apical 4-chamber view with images demonstrating the maximum diameter of the RV without foreshortening. (Figure 2) An additional RV dimension at the RV outflow tract (OT) will be measured: (1) Proximal RVOT diameter at the left parasternal long axis view for the proximal portion of the RVOT (normal <33 mm), and (2) Distal RVOT diameter at the left parasternal short axis view demonstrating RVOT at the level of the pulmonic valve (normal <27 mm). (Figure 2) RV wall thickness will be measured at the left parasternal view in diastole (normal <5 mm). In addition, right ventricular systolic function will be assessed using (1) tricuspid annular plane systolic excursion (TAPSE) and right ventricular fractional area change (FAC). (Figure 2)

$$Right\ Ventricular\ Fractional\ Area\ Change\ (\%) = 100 \times \frac{RV\ end\ diastolic\ area - RV\ end\ systolic\ area}{RV\ end\ diastolic\ area}$$

Right ventricular systolic pressure (RVSP) will be determined using continuous-wave Doppler echocardiography. Additional parameters to estimate RA will include (1) inferior vena cava diameter and (2) Caval index that measures the respiratory collapse of the inferior vena cava.[19 20] Additional echocardiographic signs of pulmonary hypertension include (1) Dilated RV with RV to left ventricular (LV) basal diameter >1.0; (2) Flattening of the interventricular septum; (3) Dilated pulmonary artery; (4) Dilated inferior vena cava; and (5) Dilated RA. The echocardiographic probability of pulmonary hypertension will be classified as low, intermediate

or high according to the 2015 European Society of Cardiology /European Respiratory Society Guidelines for the Diagnosis and Treatment of PAH.[5] (Table 3)

Right Heart Catheterization

In accordance with the guidelines,[5] standard right heart catheterization will be performed in participants with a high echocardiographic probability of pulmonary hypertension. PAH is defined as mean pulmonary artery pressure > 25 mmHg with a pulmonary capillary wedge pressure (PCWP) ≤15 mmHg and pulmonary vascular resistance (PVR) > 3 WU obtained at right heart catheterization. Pulmonary hypertension will be further classified into the five groups according to hemodynamic findings of right heart catheterization, clinical presentation, and other pathological findings.[5]

Study Measures

The primary measures will be the diagnosis and the types of pulmonary hypertension in methamphetamine users. The prevalence of PAH amongst methamphetamine users will be determined. The secondary measures will be the risk factors for occurrence of PAH in methamphetamine users.

Sample size calculation

As there are no clinical data to enable estimation of the prevalence of pulmonary hypertension amongst methamphetamine users, a convenience sample will be used in the SOPHMA study. In 2017, the number of reported methamphetamine users in Hong Kong was 1,727. Given that the estimated proportion of dependent users in a specialist substance abuse clinic is

approximately 5-10%, the target sample size will be 200.

Patient and public involvement

The study designed was informed by discussion with management and practitioners of the substance abuse clinic in Queen Mary Hospital, Dr Wai-Chi Chan and Dr Albert-Kar-Kin Chung. The study design relied on their advices, as they have both close interactions with the patients and understanding of their medical conditions, and can represent patients' wishes and medical needs. Their advices also determined our patient recruitment strategy of applying screening to unselected adult methamphetamine users, which would be most appropriate for our study objectives.

Once the study is completed, we will disseminate findings to the patients. Patients who are diagnosed to have PAH will be referred to local cardiology clinics for long-term follow-up.

Statistical analysis

Continuous variables will be expressed as mean ± SD. Statistical comparisons between methamphetamine users with and without PAH will be performed using Student's t test or Fisher's exact test, as appropriate. Hazard ratio (HR) and 95% confidence intervals for each variable to predict PAH will be determined using a multivariate Cox regression model with a p value <0.1 for inclusion. The prognostic performance of models in predicting PAH will be assessed using c-statistics. C-statistic for receiver operating characteristic curve will be calculated using Analyze-It for Excel with the Delong-Delong comparison for c-statistic. A p value <0.05 will be considered significant. Calculations will be performed using SPSS software (version 12.0) and MedCal (version 13.1.2).

ETHICS AND DISSEMINATION

The study protocol has been approved by the Institutional Review Board of The University of Hong Kong and Hong Kong West Cluster, Hospital Authority, Hong Kong. Written consent will be obtained from each participant and the study will be performed in accordance with the ethical standards laid down in the Declaration of Helsinki and its later amendments.

PAH is a devastating, often life-threatening condition. In randomized control trials, new pharmacological treatments specifically targeting the molecular pathway of PAH have been shown to improve the morbidity and mortality of patients with PAH. Nonetheless in real-world clinical registries, the prognosis of PAH remains poor. This is at least partly related to the delay in diagnosis. Early diagnosis of PAH is associated with improved long-term survival. As a result, detection of PAH in high-risk patients such as those with connective tissue disease[12] has been regarded as a crucial next step to further improve the clinical outcomes. In the DETECT study of systemic sclerosis patients, a multi-modal approach that included echocardiography and biomarker was shown to be a sensitive, non-invasive means to identify PAH with minimal false negative results,[8] and is recommended for screening of PAH in patients with systemic sclerosis.[5] Nonetheless apart from the setting of systemic sclerosis, systematic screening has not been recommended for other candidate patient groups potentially at high risk of pulmonary artery hypertension.

In the REVEAL registry, drug-induced PAH accounted for 10.5% of all cases of pulmonary hypertension.[6] Historically, drugs used in the treatment of anorexia that have a chemical structure

similar to amphetamines such as aminorex, fenfluramine, benfluorex, and phenylpropanolamine have been shown by several epidemiological studies to be associated with the development of PAH. Illicit use of methamphetamine, currently classified as a "likely" cause of drug-induced PAH by international guidelines,[5] has been reported in 33.8 million individuals globally.[1] Nonetheless due to the unknown prevalence of PAH in methamphetamine users, it remains uncertain whether a systematic screening approach is appropriate to detect PAH in the early asymptomatic phase. Experience obtained from PAH screening in systemic sclerosis may serve as a model for PAH screening among methamphetamine users.

In this cross-sectional screening study, we will apply a current guideline-recommended PAH screening algorithm for systemic sclerosis to a cohort of unselected methamphetamine users. The strength of the SOPHMA study is that we will be the first group to utilize an established systematic approach to screen for PAH and study the risk factors for PAH among methamphetamine users. The weakness of this study is that only those with a high echocardiographic probability of PAH will undergo right heart catheterization. This is because right heart catheterization is not without risk, and current guidelines advocate limiting the procedure to those with a high probability of PAH based on echocardiographic measurements.[5] The major drawback of this approach is that false negative results based on a low and/or intermediate echocardiographic probability of PAH may under-estimate the "true" prevalence of PAH in methamphetamine users. Nevertheless we believe that the false negative rate will be low since the DETECT study confirmed that non-invasive assessment is capable of identifying PAH in systemic sclerosis patients with minimal false negatives.[8]

In summary, the SOPHMA study will explore the application of the screening strategy for PAH that is currently recommended for systemic sclerosis to methamphetamine users. This study will identify the prevalence and types of PAH in methamphetamine users. The study will also identify individual risk factors for the occurrence of PAH in methamphetamine users, followed by prediction model development. The SOPHMA study will be an important contribution to the methamphetamine-related PAH literature as one of the first systematic screening studies to use an established screening protocol. Ultimately, this study will provide the necessary evidence to establish universal guidelines for screening of PAH in methamphetamine users.

Conflicts of Interest

None.

Acknowledgement

None.

Author Contributions

This study was jointly designed by Professor Chung-Wah Siu, Dr Wai-Chi Chan and Dr Albert-Kar-Kin Chung and prepared by Dr Yangyang Cheng and Dr Jo Jo Hai. All authors contributed by revision and critical appraisal of the manuscript.

Data Statement

Data are accessible on request.

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Table 1. Screening Procedure for Pulmonary Hypertension

Items
1. Demographic data, data pertinent to methamphetamine use and other cardiovascular risk factors/conditions
2. Standard 12-lead electrocardiogram
3. Plasma concentration of brain natriuretic peptide and other biomarkers
4. 6-minute walking distance
5. Echocardiography

Table 2. Demographic Data and Data Pertinent to Methamphetamine Use and Cardiovascular diseases

	Items
Demographic	Age Gender Quantification of history of methamphetamine use
Cardiovascular data	**Risk factors**: Hypertension, diabetes mellitus, hyperlipidemia **Diseases**: Coronary artery disease, peripheral artery disease, stroke, myocardial infarction, heart failure, atrial fibrillation, other conduction abnormalities
Renal function	Serum urea, serum creatinine, and estimated glomerular filtration rate

Table 3. Echocardiographic Probability of Pulmonary Hypertension According to [5]

RVSP (mmHg)	Peak tricuspid regurgitation velocity (m/s)	Other ECHO PAH Sign	ECHO Probability of PAH
31	2.8 or not measurable	No	Low
31	2.8 or not measurable	Yes	Intermediate
32-46	2.9-3.4	No	Intermediate
32-46	2.9-3.4	Yes	High
> 46	> 3.4	Not required	High

Abbreviations: ECHO – Echocardiography.

LEGENDS

Figure 1. Study flow. Abbreviations: BNP: Brain natriuretic peptide; ECG: electrocardiography; V/Q scan: Ventilation and perfusion scan.

Figure 2. Echocardiography view. (A) Apical 4-Chamber view for right atrial and ventricular dimension; and (B) Right Ventricular Fractional Area Change: Yellow area: right ventricular (RV) end-diastolic area, and **Red area:** RV end-systolic area.

$$Right\ Ventricular\ Fractional\ Area\ Change\ (\%) = 100 \times \frac{RV\ end\ diastolic\ area - RV\ end\ systolic\ area}{RV\ end\ diastolic\ area}$$

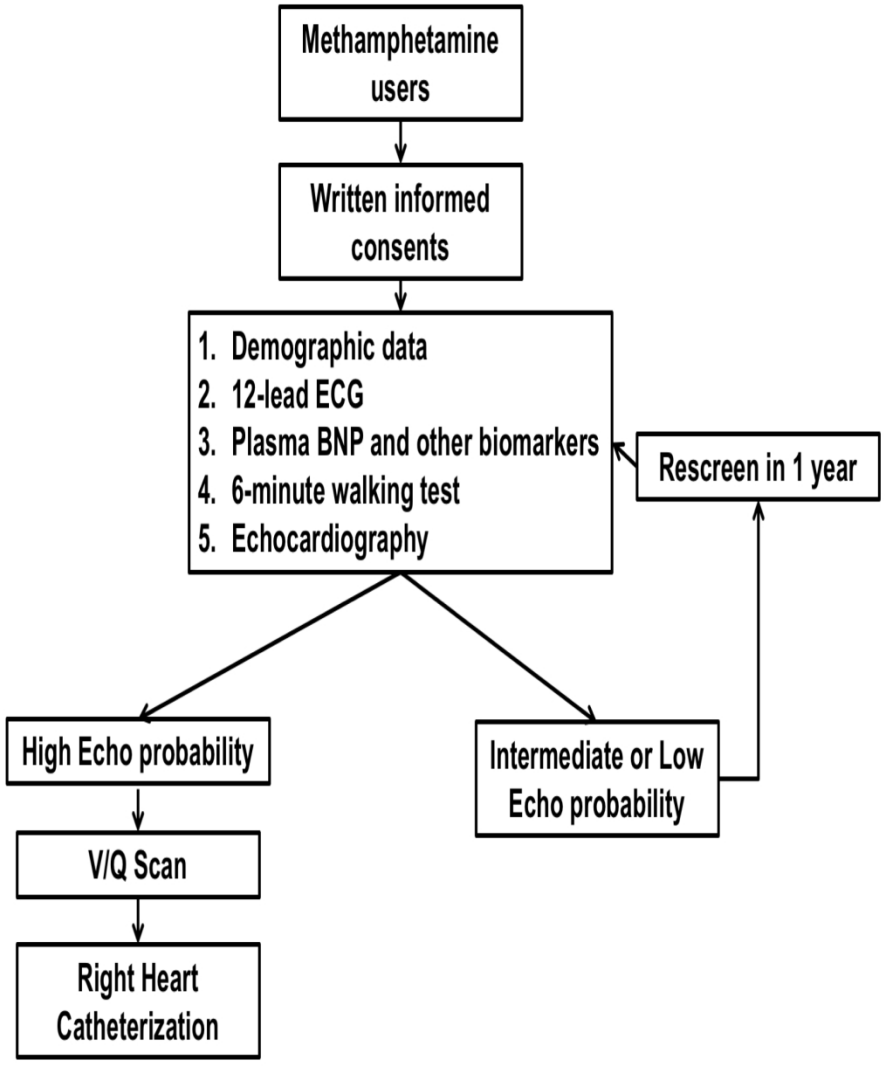

FIGURE 1

Figure 1. Study flow. Abbreviations: BNP: Brain natriuretic peptide; ECG: electrocardiography; V/Q scan: Ventilation and perfusion scan.

253x338mm (169 x 169 DPI)

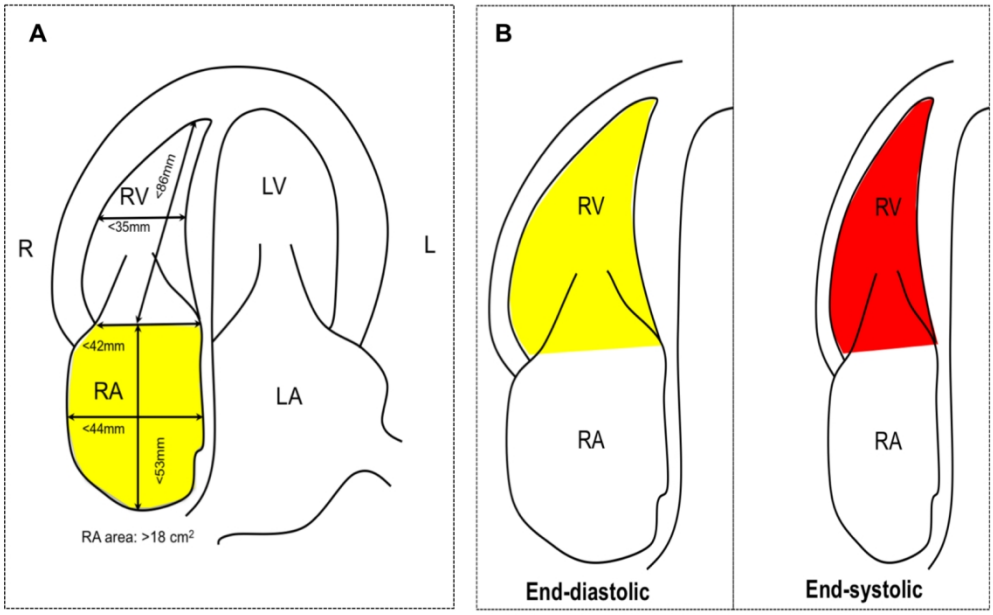

FIGURE 2

Figure 2. Echocardiography view. (A) Apical 4-Chamber view for right atrial and ventricular dimension; and (B) Right Ventricular Fractional Area Change: Yellow area: right ventricular (RV) end-diastolic area, and Red area: RV end-systolic area.
Right Ventricular Fractional Area Change (%)=100 × (RV end diastolic area-RV end systolic area)/(RV end diastolic area)

253x190mm (169 x 169 DPI)

Note from the Editors: Instructions for reviewers of study protocols

Since launching in 2011, BMJ Open has published study protocols for planned or ongoing research studies. If data collection is complete, we will not consider the manuscript.

Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicised. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study.

The scientific integrity and the credibility of the study data depend substantially on the study design and methodology, which is why the study protocol requires a thorough peer-review.

BMJ Open will consider for publication protocols for any study design, including observational studies and systematic reviews.

Some things to keep in mind when reviewing the study protocol:

- Protocol papers should report planned or ongoing studies. The dates of the study should be included in the manuscript.
- Unfortunately we are unable to customize the reviewer report form for study protocols. As such, some of the items (i.e., those pertaining to results) on the form should be scored as Not Applicable (N/A).
- While some baseline data can be presented, there should be no results or conclusions present in the study protocol.
- For studies that are ongoing, it is generally the case that very few changes can be made to the methodology. As such, requests for revisions are generally clarifications for the rationale or details relating to the methods. If there is a major flaw in the study that would prevent a sound interpretation of the data, we would expect the study protocol to be rejected.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
√ **Title and abstract**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
√ Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
√ Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
√ Study design	4	Present key elements of study design early in the paper
√ Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
√ Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
√ Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
√ Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
√ Bias	9	Describe any efforts to address potential sources of bias
√ Study size	10	Explain how the study size was arrived at
√ Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
√ Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results (Not applicable)		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for

		a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion (Not applicable)		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
√ Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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RATIONALE AND DESIGN OF A MULTI-CENTER CROSS-SECTIONAL STUDY FOR THE SCREENING OF PULMONARY HYPERTENSION IN METHAMPHETAMINE ABUSERS (SOPHMA)

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RATIONALE AND DESIGN OF A MULTI-CENTER CROSS-SECTIONAL STUDY FOR THE SCREENING OF PULMONARY HYPERTENSION IN METHAMPHETAMINE ABUSERS (SOPHMA)

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ABSTRACT

Introduction: Methamphetamine misuse is classified as a ‘‘likely’’ risk factor for pulmonary arterial hypertension (PAH). Nevertheless the actual prevalence of and a screening strategy for PAH in methamphetamine users have not been established. We plan to study the prevalence of PAH and identify its independent risk factors among methamphetamine users.

Methods and analysis: The Screening of Pulmonary Hypertension in Methamphetamine Abusers (SOPHMA) study will be a multi-center, cross-sectional screening study that will involve substance abuse clinics, hospitals and rehabilitation facilities in Hong Kong that cater to more than 20 methamphetamine users. A total of 400 patients who (1) are ≥18 years at enrolment; (2) report methamphetamine use in the last 2 years; (3) are diagnosed as methamphetamine use disorder; and (4) voluntarily agree to participate by providing written informed consent will be included. Patients will undergo standard echocardiography-based PAH screening procedures recommended for those with systemic sclerosis. Right heart catheterization will be offered to participants with intermediate or high echocardiographic probability of PAH. For participants with a low echocardiographic probability of PAH, re-screening will be performed within one year. The primary measure will be the prevalence of PAH in methamphetamine users. The secondary measures will be the risk factors and a prediction model for PAH in methamphetamine users.

Ethics and dissemination: The SOPHMA study has been approved by the institutional review board. The findings of this study will provide the necessary evidence to establish universal guidelines for screening of PAH in methamphetamine users. Our results will be disseminated through immediate feedback to study participants, press release to the general public, as well as presentation in medical conferences and publications in peer-review journals to health care providers and academia worldwide.

Keywords: methamphetamine, pulmonary hypertension, screening

STRENGTH AND LIMITATIONS

1. The SOPHMA study will be the first to evaluate the prevalence of and identify risk factors for PAH among methamphetamine users.
2. This study will apply a current guideline-recommended PAH screening algorithm for systemic sclerosis to unselected methamphetamine users.
3. The screening strategy is an echocardiography-based protocol. Right heart catheterization will be confined to those with a high echocardiographic probability of PAH in accordance with guideline recommendations.
4. The restricted application of right heart catheterization to those with high echocardiographic probability of PAH may under-estimate the "true" prevalence of PAH in methamphetamine users.

INTRODUCTION

Methamphetamine is a potent central nervous system stimulant originally prescribed for individuals with a neuropsychiatric disorder such as attention-deficit hyperactivity disorder. Due to its highly addictive nature, illicit methamphetamine use is emerging as a major public health problem worldwide. In 2013 the United Nations Office on Drugs and Crime reported that 0.7% of the global population aged between 15 and 64 years, i.e., 33.8 million individuals, reported use of methamphetamine and/or related compounds in 2010.[1] This illicit methamphetamine use is expected to increase.[1] In addition to the infamous methamphetamine use disorder, which is primarily a psychiatric condition due to the neurocognitive effects of methamphetamine,[2] methamphetamine also affects the cardiovascular system. Chronic sympathetic activation leads to hypertension, cardiac dysrhythmias, ischemic strokes, and myocardial infarction. As methamphetamine can be inhaled in a vaporized form and smoked or snorted, serious respiratory complications can also ensue including pulmonary arterial hypertension (PAH).

PAH is a devastating and often life-threatening condition. It is hemodynamically defined as an elevated mean pulmonary artery pressure ≥25 mmHg and elevated pulmonary vascular resistance ≥3 WU combined with a normal pulmonary artery wedge pressure ≤15 mmHg in the absence of significant lung disease and/or chronic thromboembolic pulmonary hypertension. The association of PAH with methamphetamine use was first described in a case report in 1993.[3] In a subsequent retrospective cohort, patients with idiopathic PAH were found to have a much higher prevalence of prior use of methamphetamine and/or its related compounds (28.9%), compared with patients with chronic thromboembolic pulmonary hypertension (4.3%) or pulmonary hypertension due to a known associated condition (3.8%).[4]

Although current international guidelines recognise methamphetamines as a "likely" cause of drug-induced PAH,[5] almost nothing is known about its prevalence and incidence amongst methamphetamine users.

In the REVEAL registry (Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension disease management),[6] a 55-center longitudinal United States-based PAH registry, the estimated 5-year survival from diagnosis of PAH was 49%. Since patients with PAH often remain asymptomatic in the early phase, the diagnosis is often made late in the course of the disease, when most small pulmonary arteries have been obliterated, rendering therapy ineffective.[7] As such, international guidelines recommend routine screening with resting transthoracic echocardiography and biomarkers to promptly detect PAH in asymptomatic high-risk individuals such as those with systemic sclerosis.[5 8] Although the prognosis of patients with methamphetamine-associated PAH appears to be much worse than for those with idiopathic PAH,[9] international guidelines[5] and expert consensus[10] have not considered screening for PAH in asymptomatic methamphetamine users. The lack of a screening effort for PAH amongst methamphetamine users is due to the unknown prevalence of PAH in this population that adversely affects the cost effectiveness of any screening procedure.[8] This hampers the prospect of identifying risk factors of PAH[11] and developing a prediction model for the occurrence of PAH in methamphetamine users.

The **S**creening **O**f **P**ulmonary **H**ypertension in **M**ethamphetamine **A**busers (**SOPHMA**) Study is a cross-sectional screening study that will apply a current guideline-recommended echocardiography-based PAH screening algorithm to a large cohort of unselected methamphetamine users in Hong Kong.[5 12] The study objectives include:

(1) To describe the prevalence of PAH amongst methamphetamine users using a current guideline-recommended echocardiography-based PAH screening algorithm

(2) To identify independent risk factors for PAH in methamphetamine users; and

(3) To develop a prediction model for PAH in methamphetamine users.

METHODS AND ANALYSIS

Study design

SOPHMA is a multi-center, cross-sectional screening study based in Hong Kong. Participating centres must have a specialized substance abuse service with a minimum of 20 methamphetamine users being actively followed up. The study protocol is summarized in Figure 1. Table 1 summarizes the five items included in the study screening procedure. According to the guidelines,[5] standard right heart catheterization will be performed in patients with intermediate or high echocardiographic probability of pulmonary hypertension. For those with a low echocardiographic probability, screening will be repeated within one year to ensure true negativity of the original scan.

Patients and Patient Recruitment strategy

Participants who fulfil the following criteria will be invited to participate in the study: (1) age ≥18 years at enrolment, (2) report of methamphetamine use in the last two years, (3) diagnosed with methamphetamine use disorder according to the Diagnostic and Statistical Manual of Mental Disorders (the 5th edition)(DSM-V),13 and (4) voluntary agreement to participate by providing written informed consent. Patients who attend the substance abuse clinic with a diagnosis of methamphetamine use disorder between 1st Jul 2019 and 30th Jun 2021 and are capable of providing an informed consent will be contacted by a research nurse. The design and objectives of the study will then be explained to the patient. An invitation information leaflet detailing the study will be provided to the candidate patients at the same time. Patients who refuse to provide written informed consent will be excluded.

Demographic and Serum Data Collection

Demographic data and a detailed history of methamphetamine use will be recorded. In addition, cardiovascular risk factors, history of other cardiovascular diseases, investigative results in the last three months including NT-proBNP, liver and renal function as well as serum urate will be recorded. Table 2 summarizes the demographic data and other cardiovascular risk factors and/or conditions to be collected.

Echocardiographic examination

Detailed quantitative transthoracic echocardiography examination including two-dimensional, M-mode, and Doppler flow studies will be performed in all patients. Standard two-dimensional and M-mode measurements will be performed according to the recommendations of the American Society of Echocardiography.[14] Valvular regurgitation will be classified as mild, moderate, or severe using a semi-quantitative method.[15] A standard Doppler echocardiographic method will be used to estimate cardiac output.[16] For calculation of cardiac output, an average of five consecutive ventricular systoles during sinus rhythm, or an average of 13 beats in case of atrial fibrillation, will be obtained.[17] Simultaneous blood pressure measurements will be recorded with a calibrated non-invasive semiautomatic device (Dinamap 1846XT; Critikon Corp., Tampa, FL) during the determination of cardiac output. Total vascular resistance (TVR) in dyne-sec/cm5 will be calculated using the following formula:

$$Total\ Vacsular\ Resistance\ (\text{dyne} - \frac{\text{sec}}{\text{cm5}}) = 80\ x \frac{mean\ arterial\ blood\ pressure\ (mmHg)}{Cardiac\ output\ (L/min)}$$

For the right heart, specific transthoracic echocardiographic measurements will be performed based on the Guidelines for the Echocardiographic Assessment of the Right Heart in Adults from the American Society of Echocardiography that are endorsed by the European Association of Echocardiography.[18] Specifically, right atrial (RA) dimension

will be assessed using RA area (normal <18 cm2), RA length (normal <53 mm) and RA diameter (normal <44mm). Right ventricular (RV) dimension will be estimated at the base (normal: <42 mm) and at the mid-level (normal: <35 mm) as well as the longitudinal dimension (normal: <86 mm) at end-diastole from a RV-focused apical 4-chamber view with images demonstrating the maximum diameter of the RV without foreshortening. (Figure 2) An additional RV dimension at the RV outflow tract (OT) will be measured: (1) Proximal RVOT diameter at the left parasternal long axis view for the proximal portion of the RVOT (normal <33 mm), and (2) Distal RVOT diameter at the left parasternal short axis view demonstrating RVOT at the level of the pulmonic valve (normal <27 mm). (Figure 2) RV wall thickness will be measured at the left parasternal view in diastole (normal <5 mm). In addition, right ventricular systolic function will be assessed using (1) tricuspid annular plane systolic excursion (TAPSE) and right ventricular fractional area change (FAC). (Figure 2)

$$Right\ Ventricular\ Fractional\ Area\ Change\ (\%) = 100 \times \frac{RV\ end\ diastolic\ area - RV\ end\ systolic\ area}{RV\ end\ diastolic\ area}$$

Right ventricular systolic pressure (RVSP) will be determined using continuous-wave Doppler echocardiography. Additional parameters to estimate RA will include (1) inferior vena cava diameter and (2) Caval index that measures the respiratory collapse of the inferior vena cava.[19 20] Additional echocardiographic signs of pulmonary hypertension include (1) Dilated RV with RV to left ventricular (LV) basal diameter >1.0; (2) Flattening of the interventricular septum; (3) Dilated pulmonary artery; (4) Dilated inferior vena cava; and (5) Dilated RA. The echocardiographic probability of pulmonary hypertension will be classified as low, intermediate or high according to the 2015 European Society of Cardiology /European Respiratory Society Guidelines for the Diagnosis and Treatment of PAH.[5] (Table 3)

Right Heart Catheterization and other investigations

In accordance with the guidelines,[5] standard right heart catheterization will be performed in participants with high echocardiographic probability of pulmonary hypertension. Pulmonary hypertension is defined by a mean pulmonary artery pressure ≥25mmHg. The type of pulmonary hypertension will be further classified into group one to group five according to hemodynamic findings of right heart catheterization, clinical presentation, radiological investigation results and other pathological findings.[5] PAH, also known as group one pulmonary hypertension, is defined by a pulmonary capillary wedge pressure (PCWP) ≤15 mmHg and pulmonary vascular resistance (PVR) >3 wood units in the absence of significant left-sided heart disease, severe lung disease or chronic thromboembolic disease. For those who have PAH diagnosed, additional workup will be performed to look for other contributory factors of PAH, including connective tissue disorder, human immunodeficiency virus infection and chronic liver disease.

Study Measures

The primary measures will be the prevalence of PAH in methamphetamine users. The secondary measures will be the risk factors for occurrence of PAH and prognostic performance and the final prediction model for PAH in methamphetamine users.

Sample size calculation

As there are no clinical data to enable estimation of the prevalence of pulmonary hypertension amongst methamphetamine users, a convenience sample will be used in the SOPHMA study. In 2017, the number of reported methamphetamine users in Hong Kong was 1,727. Given that the estimated proportion of dependent users in a specialist substance

abuse clinic is approximately 10-20%, the target sample size will be 400.

Patient and public involvement

The study designed was informed by discussion with management and practitioners of the substance abuse services in Queen Mary Hospital, Castle Peak Hospital and Kwai Chung Hospital. The study design relied on their advices, as they have both close interactions with the patients and understanding of their medical conditions, and can represent patients' wishes and medical needs. Their advices also determined our patient recruitment as well as result dissemination strategies.

Once the study is completed, we will disseminate our findings to the study participants by immediate feedback. Patients who are diagnosed to have PAH will be referred to local cardiology clinics for long-term follow-up.

Statistical analysis

Continuous variables will be expressed as mean ± standard deviation. Statistical comparisons between methamphetamine users with and without PAH will be performed using Student's t test or Fisher's exact test, as appropriate. Hazard ratio and 95% confidence intervals for each variable to predict PAH will be determined using a multivariate Cox regression model with a p value <0.1 for inclusion. The prognostic performance of models in predicting PAH will be assessed using c-statistics. C-statistic for receiver operating characteristic curve will be calculated using Analyze-It for Excel with the Delong-Delong comparison for c-statistic. A P-value <0.05 will be considered significant. Calculations will be performed using SPSS software (version 12.0) and MedCal (version 13.1.2).

ETHICS AND DISSEMINATION

The study protocol has been approved by the Institutional Review Board of The University of Hong Kong and Hong Kong West Cluster, Hospital Authority, Hong Kong. Written consent will be obtained from each participant and the study will be performed in accordance with the ethical standards laid down in the Declaration of Helsinki and its later amendments.

PAH is a devastating, often life-threatening condition. In randomized control trials, new pharmacological treatments specifically targeting the molecular pathway of PAH have been shown to improve the morbidity and mortality of patients with PAH. Nonetheless in real-world clinical registries, the prognosis of PAH remains poor. This is at least partly related to the delay in diagnosis. Early diagnosis of PAH is associated with improved long-term survival. As a result, detection of PAH in high-risk patients such as those with connective tissue disease[12] has been regarded as a crucial next step to further improve the clinical outcomes. In the DETECT study of systemic sclerosis patients, a multi-modal approach that included echocardiography and biomarker was shown to be a sensitive, non-invasive means to identify PAH with minimal false negative results,[8] and is recommended for screening of PAH in patients with systemic sclerosis.[5] Nonetheless apart from the setting of systemic sclerosis,

systematic screening has not been recommended for other candidate patient groups potentially at high risk of pulmonary artery hypertension.

In the REVEAL registry, drug-induced PAH accounted for 10.5% of all cases of pulmonary hypertension.[6] Historically, drugs used in the treatment of anorexia that have a chemical structure similar to amphetamines such as aminorex, fenfluramine, benfluorex, and phenylpropanolamine have been shown by several epidemiological studies to be associated with the development of PAH. Illicit use of methamphetamine, currently classified as a "likely" cause of drug-induced PAH by international guidelines,[5] has been reported in 33.8 million individuals globally.[1] Nonetheless due to the unknown prevalence of PAH in methamphetamine users, it remains uncertain whether a systematic screening approach is appropriate to detect PAH in the early asymptomatic phase. Experience obtained from PAH screening in systemic sclerosis may serve as a model for PAH screening among methamphetamine users.

In this cross-sectional screening study, we will apply a current guideline-recommended echocardiography-based PAH screening algorithm to a cohort of unselected methamphetamine users. The strength of the SOPHMA study is that we will be the first group to utilize an established systematic approach to screen for PAH and study the risk factors for PAH among methamphetamine users. The weakness of this study is that only those with intermediate or high echocardiographic probability of PAH will undergo right heart catheterization. This is because right heart catheterization is not without risk, and current guidelines advocate limiting the procedure to those with intermediate or high probability of PAH based on echocardiographic measurements.[5] The major drawback of this approach is that false negative results based on a low echocardiographic probability of PAH may under-estimate the "true"

prevalence of PAH in methamphetamine users. Nevertheless we believe that the false negative rate will be low since the DETECT study confirmed that non-invasive assessment is capable of identifying PAH in systemic sclerosis patients with minimal false negatives.[8]

The SOPHMA study will provide information about the prevalence of and risk factors for the occurrence of PAH in methamphetamine users, followed by development of a prediction model development. Our results will provide scientific evidence to enable psychiatric and cardiovascular professional bodies to establish universal guidelines for the screening of PAH amongst patients with methamphetamine use disorder, and form the foundation for academia to study the mechanisms, treatment and outcomes of methamphetamine-associated PAH. In addition, symptoms of PAH, such as reduced exercise tolerance and fatigability, are frequently attributed by patients and health care professionals to methamphetamine use, which can partly explain the exceptionally advanced disease status at diagnosis and poor clinical outcomes of methamphetamine-associated PAH.[9 21] The results of this study will alert patients and health care providers to this serious complication of methamphetamine use, such that patients who develop suspicious symptoms will promptly report and be referred for specialist assessment. Our results will also benefit the society by raising public awareness of this debilitating and potentially lethal consequence of methamphetamine use.

There are five key audiences for this research 1) psychiatric and cardiovascular professional bodies; 2) academia; 3) health care providers; 4) participating methamphetamine users; and 5) the general public. We will use multiple vehicles to disseminate the results of this study to our targeted audiences. First, we will present our research findings at international medical conferences and publish our results in peer-review journals. Second, we will dispense information leaflets, accompanied by in-person discussion and immediate feedback to our

study participants. Third, we will hold a press conference, followed by publication of a series of feature reports in key news media, in order to announce our results to the general public. This proactive dissemination strategy will ensure effective dissemination of our results, and is a crucial part of efforts to improve prevention and management of the condition.

In summary, the SOPHMA study will explore the application of the PAH-screening strategy that is currently recommended for high-risk patients in methamphetamine users. The findings of this study will provide the necessary evidence for professional bodies to establish universal guidelines for screening of PAH in methamphetamine users.

Conflicts of Interest

None.

Acknowledgement

None.

Author Contributions

This study was initially designed by Professor Chung-Wah Siu, Dr Wai-Chi Chan and Dr Albert-Kar-Kin Chung. Dr Duo Huang and Pak-Hei Chan contributed by performing literature review, and Dr Yangyang Cheng and Dr Jo Jo Hai jointly prepared the manuscript. Dr Chi-Kwong Tung, Dr Wan-Wan Liu and Dr Ming Lam have given invaluable comments and suggestions regarding the study design, taken into account the logistics and feasibility of the

study, and result dissemination strategies. Dr Jo-Jo Hai was responsible for coordinating all parties, holding meetings and discussions, as well as incorporating all comments into the manuscript. All authors contributed by revision and critical appraisal of the manuscript.

Data Statement

Data are accessible on request.

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Table 1. Screening Procedure for Pulmonary Hypertension

Items
1. Demographic data, data pertinent to methamphetamine use and other cardiovascular risk factors/conditions
2. Standard 12-lead electrocardiogram
3. Plasma concentration of brain natriuretic peptide and other biomarkers
4. 6-minute walking distance
5. Echocardiography

Table 2. Demographic Data and Data Pertinent to Methamphetamine Use and Cardiovascular diseases

	Items
Demographic	Age, gender
Drug History	Quantification of methamphetamine use: duration of regular use, time of first and last use, frequency of use, routes of administration, quantity consumed per day (if available)
	Documentation and quantification of other regularly used drugs, including all self-purchased, prescribed or over-the-counter medications
Symptoms	Shortness of breath, chest pain, syncope, presyncope, dizziness, decreased exercise tolerance, bilateral lower limb swelling, New York Heart Association classification
Cardiovascular risk factors and diseases	Risk factors: Hypertension, diabetes mellitus, hyperlipidemia, smoking, alcohol use
	Diseases: Coronary artery disease, peripheral artery disease, stroke, myocardial infarction, heart failure, atrial fibrillation, other conduction abnormalities, prior deep vein thrombosis / pulmonary embolism
Blood tests	Complete blood count, renal function test, liver function test, NT-pro B-natriuretic peptide/ B-natriuretic peptide, high-sensitive troponin I, creatine kinase/creatine kinase-MB, urate

Table 3. Echocardiographic Probability of Pulmonary Hypertension[5]

RVSP (mmHg)	Peak tricuspid regurgitation velocity (m/s)	Other ECHO PAH Sign	ECHO Probability of PAH
31	2.8 or not measurable	No	Low
31	2.8 or not measurable	Yes	Intermediate
32-46	2.9-3.4	No	Intermediate
32-46	2.9-3.4	Yes	High
> 46	> 3.4	Not required	High

Abbreviations: ECHO – Echocardiography.

LEGENDS

Figure 1. Study flow. Abbreviations: BNP: Brain natriuretic peptide; ECG: electrocardiography; V/Q scan: Ventilation and perfusion scan.

Figure 2. Echocardiography view. (A) Apical 4-Chamber view for right atrial and ventricular dimension; and (B) Right Ventricular Fractional Area Change: Yellow area: right ventricular (RV) end-diastolic area, and **Red area:** RV end-systolic area.

$$Right\ Ventricular\ Fractional\ Area\ Change\ (\%) = 100 \times \frac{RV\ end\ diastolic\ area - RV\ end\ systolic\ area}{RV\ end\ diastolic\ area}$$

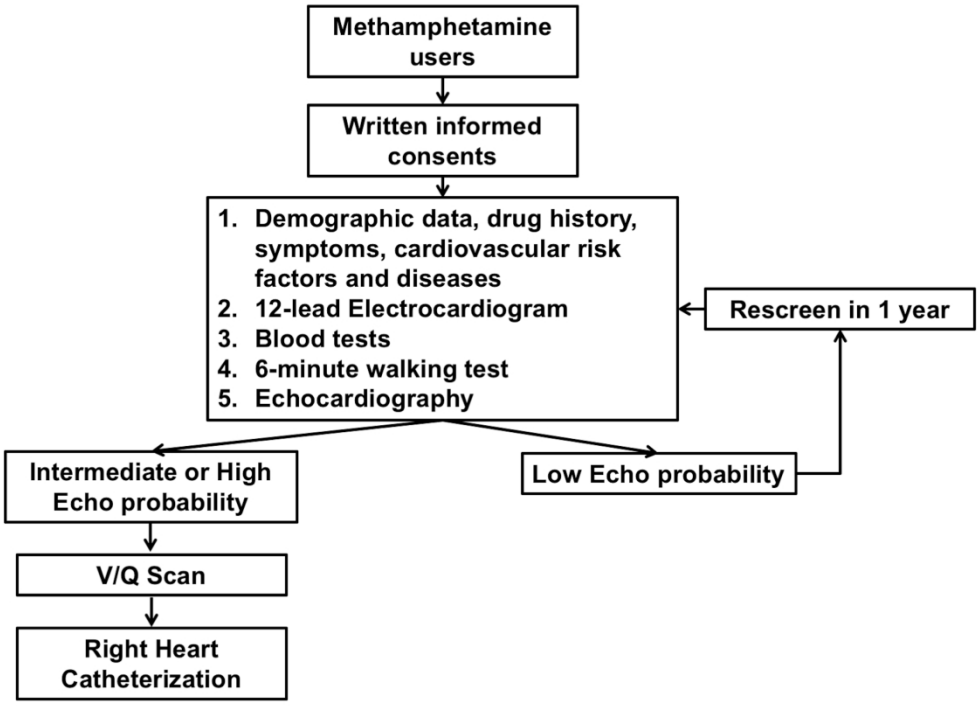

Figure 1. Study flow. Abbreviations: BNP: Brain natriuretic peptide; ECG: electrocardiography; V/Q scan: Ventilation and perfusion scan.

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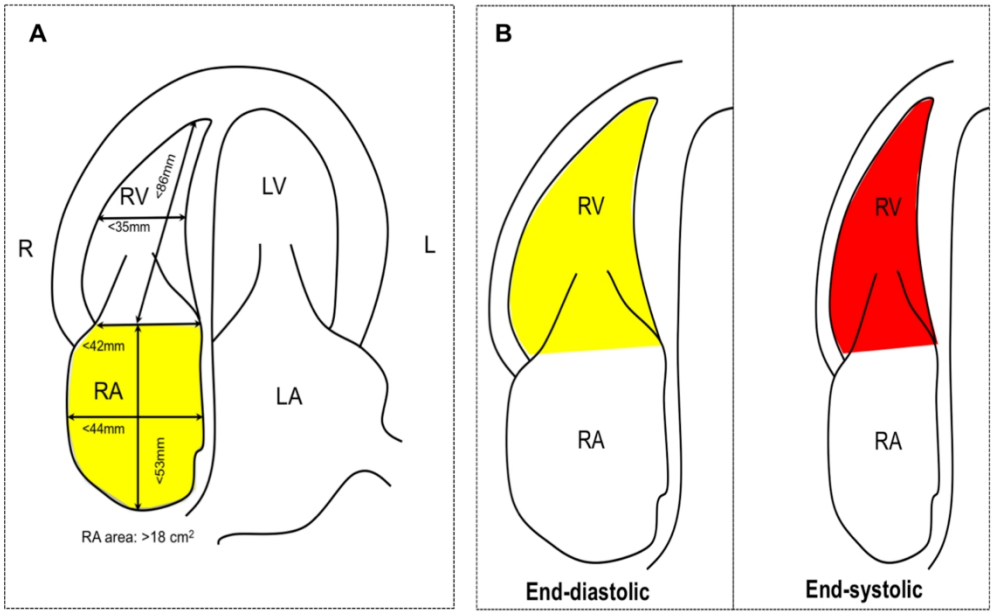

Figure 2

Figure 2. Echocardiography view. (A) Apical 4-Chamber view for right atrial and ventricular dimension; and (B) Right Ventricular Fractional Area Change: Yellow area: right ventricular (RV) end-diastolic area, and Red area: RV end-systolic area.
Right Ventricular Fractional Area Change (%)=100 × (RV end diastolic area-RV end systolic area)/(RV end diastolic area)

253x190mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract *(Title page)*
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found *(Page 1)*
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported *(Page 4-5)*
Objectives	3	State specific objectives, including any prespecified hypotheses *(Page 6)*
Methods		
Study design	4	Present key elements of study design early in the paper *(Page 7)*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection *(Page 7-11)*
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants *(Page 7)*
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable *(Page 10-11)*
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group *(Page 8-11)*
Bias	9	Describe any efforts to address potential sources of bias *(N/A)*
Study size	10	Explain how the study size was arrived at *(Page 11)*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why *(Page 12)*
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding *(Page 12)*
		(*b*) Describe any methods used to examine subgroups and interactions *(N/A)*
		(*c*) Explain how missing data were addressed *(N/A)*
		(*d*) If applicable, describe analytical methods taking account of sampling strategy *(N/A)*
		(*e*) Describe any sensitivity analyses *(N/A)*
Results *(N/A)*		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion *(N/A)*		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information *(Title page)*		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.