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EDITORIAL

Predictive power of statistical significance

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Abstract

A statistically significant research finding should not be defined as a *P*-value of 0.05 or less, because this definition does not take into account study power. Statistical significance was originally defined by Fisher RA as a *P*-value of 0.05 or less. According to Fisher, any finding that is likely to occur by random variation no more than 1 in 20 times is considered significant. Neyman J and Pearson ES subsequently argued that Fisher's definition was incomplete. They proposed that statistical significance could only be determined by analyzing the chance of incorrectly considering a study finding was significant (a Type Ⅰ error) or incorrectly considering a study finding was insignificant (a Type Ⅱ error). Their definition of statistical significance is also incomplete because the error rates are considered separately, not together. A better definition of statistical significance is the positive predictive value of a *P*-value, which is equal to the power divided by the sum of power and the *P*-value. This definition is more complete and relevant than Fisher's or Neyman-Peason's definitions, because it takes into account both concepts of statistical significance. Using this definition, a statistically significant finding requires a *P*-value of 0.05 or less when the power is at least 95%, and a *P*-value of 0.032 or less when the power is 60%. To achieve statistical significance, *P*-values must be adjusted downward as the study power decreases.

Key words: Statistical significance; Positive predictive value; Biostatistics; Clinical significance; Power

Core tip: Statistical significance is currently defined as a *P*-value of 0.05 or less, however, this definition is inadequate because of the effect of study power. A better definition of statistical significance is based upon the *P*-value's positive predictive value. To achieve statistical significance using this definition, the power divided by the sum of power plus the *P*-value must be 95% or greater.

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INTRODUCTION

Scientific research has long utilized and accepted that a research finding is statistically significant if the likelihood of observing the statistical significance equates to $P < 0.05$. In other words, the result could be attributed to luck less than 1 in 20 times. If we are testing for example, effects of drug A on effect B, we could stratify groups into those receiving therapy *vs* those taking placebo *vs* no pharmacological intervention. If the data resulted in a *P*-value less than 0.05, under the generally accepted definition, this would suggest that our results are statistically significant. However, it could be equally argued that had it resulted in a *P*-value of 0.06, or just above the generally accepted cutoff of 0.05, it is still statistically significant, but to a slightly lesser degree - an index of statistical significance rather than a dichotomous yes or no. In that case, further testing may be indicated to validate the results but perhaps not enough evidence to outright conclude that the null hypothesis, drug A has no effect, is accurate in this sense.

The originator of this idea of a statistical threshold was the famous statistician R. A. Fisher who in his book Statistical Methods for Research Workers, first proposed hypothesis testing using an analysis of variance *P* value[1]. In his words, the importance of statistical significance in biological investigation is to "prevent us being deceived by accidental occurrences" which are "not the causes we wish to study, or are trying to detect, but a combination of the many other circumstances which we can not control"[2]. His argument was that $P \leqslant 0.05$ was a convenient level of standardization to hold researchers to, but that it is not a definitive rule as an arbitrary number. It is ultimately the responsibility of the investigator to evaluate the significance of their obtained data and *P*-value. For example, in some cases, a *P*-value of 0.05 may indicate further investigation is warranted while in others that may suffice.

There were however, opposing viewpoints to this idea, namely that of Neyman J and Pearson ES who argued for more for a "hypothesis testing" rather than "significance testing" as Fisher had postulated[3]. Neyman and Pearson[4] raised the question that Fisher failed to, namely that with data interpretation there may be not only a type I error, but a type II error (accepting the null hypothesis when it should in fact be rejected). They famously stated "Without hoping to know whether each separate hypothesis is true or false, we may search for rules to govern our behavior with regard to them, in following which we insure that, in the long run of experience, we shall not be too often wrong"[4]. Part of the Neyman-Pearson approach includes researchers assigning prior to an experiment, the alternative hypothesis which should be specific such that drug X has Y effect by 30%[5]. This hypothesis is later accepted or rejected based on the *P*-value whose threshold was arbitrarily set at 0.05.

These two viewpoints between Neyman-Pearson and the more subjective view of Fisher were heavily debated and are ultimately recognized as either the Neyman-Pearson approach or the Fisher approach. In today's academic setting, the determination of statistical variance with a *P*-value has truly become dichotomous, either rejection or acceptance based on $P < 0.05$, rather than more of an index of suspicion as Fisher had originally proposed. However, an approach of confidence based on the *P*-value could be beneficial rather than a definitive decision based on an arbitrary cutoff.

The meaning and use of statistical significance as originally defined by Fisher RA, Jerzy Neyman and Egon Pearson has undergone little change in the almost 100 years since originally proposed. Statistical significance as original proposed by Fisher's *P*-value was the determination of whether or not a finding was unusual and worthy of further investigation. The Neyman-Pearson proposal was similar but slightly different. They proposed the concepts of alpha and beta with the alpha level representing the chance of erroneously thinking there is a significant finding (a Type Ⅰ error) and the beta level representing the chance of erroneously thinking there is no significant finding (a Type Ⅱ error) in the data observed[6].

CLASSICAL STATISTICAL SIGNIFICANCE

Statistical significance as currently used represents the chance that the null hypothesis is not true as defined by the *P*-value. The classic definition of a statistically significant result is when the *P*-value is less than or equal to 0.05, meaning that there is at most a one in twenty chance that the test statistic found is due to normal variation of the null hypothesis[2]. So when researchers state that their findings are "statistically significant" what they mean is that if in reality there was no difference between the groups studied, their findings would randomly occur at most only once out of twenty trials.

For example, consider an experiment in which there is no true difference between a placebo and an experimental drug. Because of normal random variation, a frequency distribution graph representing the difference between subjects taking a placebo compared with those taking the experimental drug typically forms a bell shaped curve[7]. When there is no true difference between the placebo and the experimental drug, small differences will occur frequently and cluster around zero, the center of the peak of the curve. Relatively large differences will also occur, albeit infrequently, and these results are represented by the upper and lower tails of the graph. Assuming the entire area under the bell shaped curve equals 1, as represented in Figure 1,

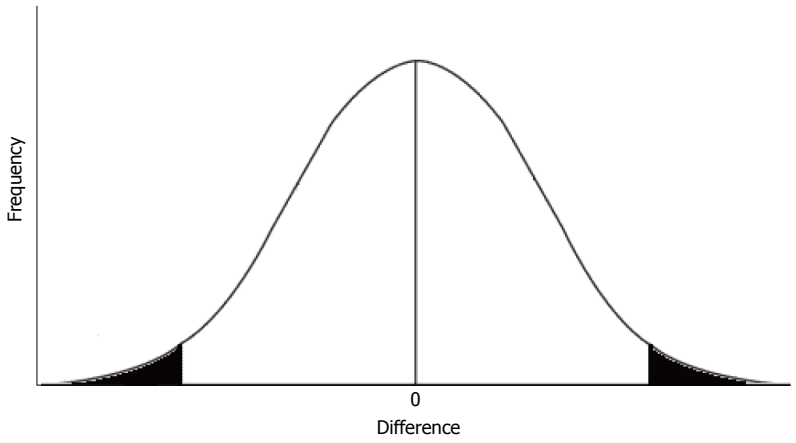

Figure 1 According to the classical definition, research findings are considered statistically significant when the difference observed falls in the upper or lower tails of the frequency distribution, represented above in black.

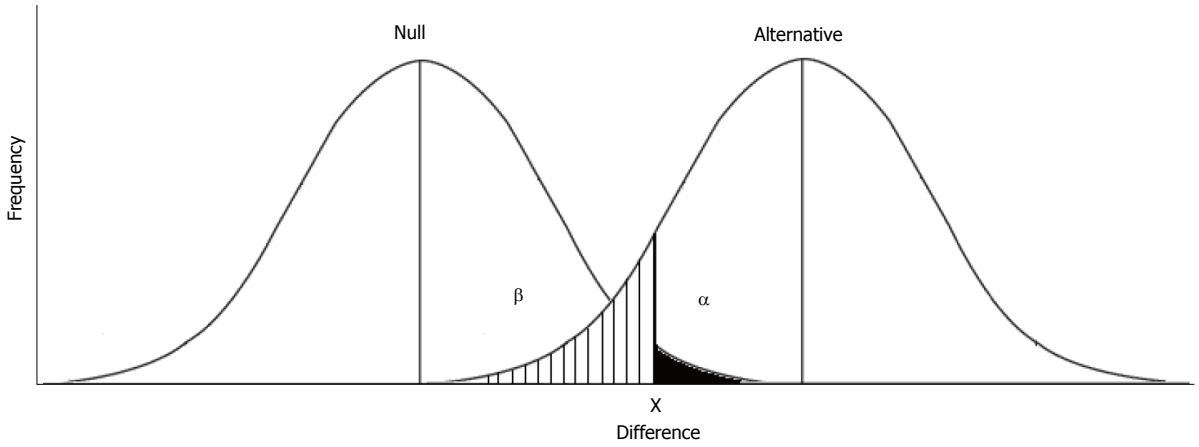

Figure 2 If the observed difference is greater than x, then we consider that the finding is statistically significant and the null hypothesis is rejected. If the difference found is less than x, then we accept the null hypothesis and reject the alternative hypothesis. The area in black represents a Type I error which occurs when the difference is greater than x, but the null hypothesis is in fact true. The lined area represents a Type II error which occurs when the difference found is less than x, but the alternative hypothesis is in fact true.

the findings are assumed to be statistically significant when the difference found falls in either the lower or upper 2.5% of the frequency distribution[8].

Note that the classical definition of statistical significance according to Fisher relies only upon a single frequency distribution curve, representing the null hypothesis that no true difference exists between the two groups observed[9]. Fisher's approach makes the primary assumption that only one group exists, as represented by a single frequency distribution curve, and *P*-values (the likelihood of a large difference being observed) define statistical significance. The Neyman-Pearson approach is slightly different, in that the primary assumption is that two groups exist, and two frequency distributions are necessary[10]. In this approach, the tail of the frequency distribution representing the null hypothesis (no difference) is represented by alpha (α). Similar to the *P*-value, alpha represents the chance of rejecting the null hypothesis when in fact it is true, a Type Ⅰ error[11]. The tail of the frequency distribution representing the alternative hypothesis (a true difference exists) is represented by beta (β). Beta represents the chance of rejecting the alternative hypothesis when in fact it is true, a Type Ⅱ error. If we are doing a one-tailed comparison, *e.g.*, when we assume the experimental drug will improve but not hurt patients, alpha and beta can be visualized in Figure 2. The area in black represents a Type Ⅰ error and the lined area represents a Type Ⅱ error.

A NEW DEFINITION OF STATISTICAL SIGNIFICANCE

It is time that the statistical significance be defined not just as the chance that the null hypothesis is not true (a low *P*-value), or the likelihood of error when accepting (α) or rejecting (β) the null hypothesis. While these statistics help us evaluate research data, they do not give us the odds of being right or wrong, which requires that we analyze both the *P*-value with β together[12].

While it is helpful to visualize the concepts of alpha and beta on frequency distribution graphs, it is

Table 1 Statistically significant research findings can represent a true positive or false positive

		Reality	
Study findings		Alternative hypothesis true	Null hypothesis true
	Significant *P*-value ⩽ 0.05	True positive	False positive
	Insignificant *P*-value > 0.05	False negative	True negative

Similarly, statistically insignificant findings may represent a true or false negative.

Table 2 When the *P*-value is utilized to determine whether or not a finding is statistically significant, 1-beta represents the sensitivity for identifying the alternative hypothesis, and 1-alpha represents the specificity

		Reality	
Study findings		Alternative hypothesis true	Null hypothesis true
	Significant *P*-value ⩽ 0.05	1 - beta (power)	Alpha (exact *P*-value)
	Insignificant *P*-value > 0.05	Beta	1 - alpha

Table 3 A Type Ⅰ error corresponds to 1-specificity and a Type Ⅱ error corresponds to 1-sensitivity when study findings are determined to be significant or insignificant based upon the *P*-value

		Reality	
Study findings		Alternative hypothesis true	Null hypothesis true
	Significant *P*-value ⩽ 0.05	Correct	Type Ⅰ error
	Insignificant *P*-value > 0.05	Type Ⅱ error	Correct

Table 4 This 2 × 2 contingency table shows the corresponding values for a research study where a study finding is determined to be significant based upon a *P*-value of 0.05 and when the study's power is 80%

		Reality	
Study findings		Alternative hypothesis true	Null hypothesis true
	Significant *P*-value ⩽ 0.05	0.8	0.05
	Insignificant *P*-value > 0.05	0.2	0.95

additionally illuminating to compare these concepts with sensitivity, specificity, and predictive values obtained from 2 × 2 contingency tables. In Table 1, the rows represent our statistical test results, and the columns represent what is actually true. Row 1 represents the situation when our data analysis results in a *P*-value of ⩽ 0.05, and row 2 represents the situation when our analysis results in a *P*-value of > 0.05. The columns represent reality. Column 1 represents the situation when the alternative hypothesis is in reality true, and column 2 represents the situation when the null hypothesis in reality is true.

In Table 1, row 1 column 1 are the true positives because the *P*-value is ⩽ 0.05 and the alternative hypothesis is true. Row 1 column 2 are false positives, because even though the *P*-value is ⩽ 0.05, the reality is that there is no significant difference and the null hypothesis is true. Similarly, row 2 column 1 are the false negatives because the *P*-value is insignificant (*P* > 0.05) but in reality the alternative hypothesis is true. Row 2 column 2 are the true negatives because the *P*-value is insignificant and the null hypothesis is true.

Table 2 shows our findings in terms of alpha and beta. In this case, alpha represents the exact *P*-value, not just whether or not the *P*-value is ⩽ 0.05. Beta is not only the chance of a Type Ⅱ error (a false negative), it is used to determine the study's power which is simply equal to 1 - beta. Table 3 shows the same information in another way, showing the situations in which our test of statistical significance, the *P*-value, is in fact correct or is in error.

When we know beta and alpha, or alternatively the *P*-value and power of the study, we can fill out the contingency table and answer our real question of how likely is it that our findings represent the truth. Statistical power, equal to 1 - beta, is typically set in advance to help determine sample size. A typical level recommended for power is 0.80[13]. Table 4 is an example 2 × 2 contingency table in the which the study has a power of 0.80 and the analysis finds a statistically significant result of *P* = 0.05. In this situation, the sensitivity of the test statistic equals the power, or 0.8/(0.8 + 0.2). The specificity of the test statistic is 1 minus alpha, or 0.95/(0.05 + 0.95). Our positive predictive value is power divided by the sum of power and the exact *P*-value, or 0.80/(0.80 + 0.05). The negative predictive value is the specificity divided by the sum of the specificity and beta, or 0.95/(0.95 + 0.20).

To be 95% confident that the *P*-value represents a statistically significant result, the positive predictive value must be 95% or greater. In the standard situation where the study power is 0.80, a *P*-value of 0.42 or less is required to achieve this level of confidence. As shown in Table 5, a power of 0.95 is required for a *P*-value of 0.05 to indicate a 95% or greater confidence that the study's findings are statistically significant. If the power falls to 90%, a *P*-value of 0.047 or less is required to be 95% confident that the alternative hypothesis is true (*i.e.*, a 95% positive predictive value). If the power is only 60%, then a *P*-value of 0.032 or less is required to be 95% confident that the alternative hypothesis is true. To determine how likely a study's findings represent the truth, determine the positive predictive value (PPV) of the test statistic:

PPV = power/(power + *P*-value)

To determine the required *P*-value to achieve a 95%

Table 5 *P*-values corrected for study power

Study power	*P*-value
0.95	0.05
0.9	0.047
0.85	0.045
0.8	0.042
0.75	0.039
0.7	0.037
0.65	0.034
0.6	0.032

PPV:

P-value = (power - 0.95 * power)/0.95

In the situation where the *P*-value is greater than the cutoff values determined by the preceding method, it is helpful to determine just how confident we can be that the null hypothesis is correct. This simply entails calculating the negative predictive value of the test statistic:

NPV = (1 - alpha)/(1 + beta - alpha)

Finally, using this method we can determine the overall accuracy of a research study. Prior to collecting and analyzing the research data, pre-set values are determined for power and a cutoff *P*-value for statistical significance. If we want to be 95% confident that a research study will correctly identify reality, a pre-set power of 95% along with a pre-set cutoff *P*-value of 0.05 is required. At a pre-set power of 90%, a pre-set cutoff *P*-value of 0.01 is required. When the pre-set power is 80% or less, the maximum confidence in the accuracy of the study findings is at most 90% even when a pre-set *P*-value cutoff is extremely low. To determine the maximum level of confidence a study can have at a specific level of power and cutoff *P*-value (alpha), calculate the accuracy:

Accuracy = (1 + power - alpha)/2

CONCLUSION

Statistical significance has for too long been broadly defined as a *P*-value of 0.05 or less[14]. Using the *P*-value alone can be misleading because its calculation does not take into account the effect of study power upon the likelihood that the *P*-value represents normal variation or a true difference in study populations[15]. If we want to be at least 95% confident that a research study has identified a true difference in study populations, the power must be at least 95%. If the power is lower, the required *P*-value to indicate a statistically significant result needs to be adjusted downward according to the formula *P*-value = (power - 0.95*power)/0.95. Furthermore, by using the positive predictive value of the *P*-value, not just the *P*-value alone, researchers and readers are able to better understand the level of confidence they can have in the findings and better assess clinical relevance[16]. Only when the power of a study is at least 95% does a *P*-value of 0.05 or less indicate a statistically significant result.

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REVIEW

Shortness of breath in clinical practice: A case for left atrial function and exercise stress testing for a comprehensive diastolic heart failure workup

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Abstract

The symptom cluster of shortness of breath (SOB) contributes significantly to the outpatient workload of cardiology services. The workup of these patients includes blood chemistry and biomarkers, imaging and functional testing of the heart and lungs. A diagnosis of diastolic heart failure is inferred through the exclusion of systolic abnormalities, a normal pulmonary function test and normal hemoglobin, coupled with diastolic abnormalities on echocardiography. Differentiating confounders such as obesity or deconditioning in a patient with diastolic abnormalities is difficult. While the most recent guidelines provide more avenues for diagnosis, such as incorporating the left atrial size, little emphasis is given to understanding left atrial function, which contributes to at least 25% of diastolic left ventricular filling; additionally, exercise stress testing to elicit symptoms and test the dynamics of diastolic parameters, especially when access to the "gold standard" invasive tests is lacking, presents clinical translational gaps. It is thus important in diastolic heart failure work up to understand left atrial mechanics

and the role of exercise testing to build a comprehensive argument for the diagnosis of diastolic heart failure in a patient presenting with SOB.

Key words: Diastolic heart failure; Exercise stress test; Left atrium; Shortness of breath; Work-up

Core tip: Shortness of breath is a common clinical complaint. Etiologies such as systolic heart failure, obstructive airways disease or anemia have clear and reproducible physiological changes detectable through routine diagnostic tests. Diastolic heart failure (DHF) is often a diagnosis of exclusion. In the absence of directly demonstrating an elevation of left ventricular end diastolic pressures at rest or exercise, DHF is inferred by a combination of symptoms and resting echocardiography findings. We discuss the importance of a wider consideration, *e.g.*, left atrium function and exercise stress testing, in DHF work-up.

Iyngkaran P, Anavekar NS, Neil C, Thomas L, Hare DL. Shortness of breath in clinical practice: A case for left atrial function and exercise stress testing for a comprehensive diastolic heart failure workup. *World J Methodol* 2017; 7(4): 117-128 Available from: URL: http://www.wjgnet.com/2222-0682/full/v7/i4/117.htm DOI: http://dx.doi.org/10.5662/wjm.v7.i4.117

INTRODUCTION

Most cardiological services are faced with a large number of referrals to diagnose and manage the symptom cluster of dyspnea or shortness of breath (SOB). Broadly the etiologies can be cardiac, respiratory, haematological, due to obesity or physical deconditioning. When a cardiac cause is considered likely, imaging modalities such as echocardiography and occasionally cardiac magnetic resonance imaging can rule out systolic heart failure or heart failure with reduced ejection fraction (SHF/HFrEF). Diastolic heart failure or heart failure with preserved ejection fraction (DHF/HFpEF) can be inferred, but requires greater analysis. Exercise stress protocols are also receiving greater attention for diagnosis of HFpEF.

To understand the controversies in DHF it is important to go back to the basics. HF is defined as "a clinical syndrome characterized by typical symptoms (*e.g.,* breathlessness, ankle swelling and fatigue) that may be accompanied by signs (*e.g.,* elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress"[1]. From this, four points are important in the work-up of patients suspected with DHF syndrome: (1) Chronic functional SOB, is the main reason for seeking medical care, however asymptomatic structural changes can also be detected. The correlation of changes at rest and with exercise with or without symptoms are yet to be adequately clarified; (2) in presentations with acute SOB admissions, risk stratifying diastolic abnormalities to a clinical course is also problematic[2,3]; for example are the observed changes age related or evidence of diastolic dysfunction contributing to DHF; (3) three conditions must be satisfied to rule in the diagnosis of HFpEF: Clinical symptoms of heart failure; normal or mildly abnormal systolic function [eft ventricular ejection fraction (LVEF) > 50%]; and demonstration of diastolic abnormalities in left ventricular (LV) relaxation and filling, and stiffness manifesting as increased LV filling pressures (invasively measured as LV end diastolic pressure > 16 mmHg (LVEDP) or mean pulmonary capillary wedge pressure or mean left atrial (LA) pressure > 12 mmHg), at rest or with exercise[2,4]; and (4) demonstrating altered LV pathophysiology in the "resting state" are better established, while evaluation of dynamic diastolic changes (*i.e.,* during exercise) and alterations in left atrium (LA) metrics (*i.e.,* volume or function parameters), have not be given enough emphasis.

The incidence of HFpEF appears to be increasing relative to HFrEF. Combined data among HF presentations reveals an average prevalence of 54% (range 40%-71%)[5]. The etiology and pathophysiological basis also appears different. Patients tend to be older with greater burden of co-morbidities[6,7]. Cardiovascular and non-cardiovascular mortality is increased, although lower than HFrEF. However, survival trends are improving with HFrEF but not HFpEF[8-11]. There have been numerous publications and guideline updates that provide a synopsis of pathophysiology[12-14], clinical correlation and pathways for assessment of DHF[1-3,15] and management[16]. This review is focused on establishing the importance of LA function and exercise testing in the workup of a patient presenting with SOB. We also explore the rationale for including LA metrics under the umbrella of the DHF syndrome focusing on published work using echocardiography as the imaging modality (DHF and HFpEF are used interchangeably, where DHF is used in context of the syndrome and HFpEF in the scientific commentary).

LEFT ATRIAL ANATOMY, PHYSIOLOGY AND FUNCTION IN HEALTH AND DISEASE

The LA is predominately composed of overlapping and varyingly aligned layers of muscle fibers that have marked variation in thickness but is overall, significantly thinner than the LV. The left coronary artery and oblique vein, which drain into the coronary sinus, are the main arterial and venous blood vessels. Specifics on LA anatomy have been previously detailed[17,18]. The LA has four important mechanical functions across three phases (Figure 1): (1) A reservoir (phase) to receive blood and store kinetic energy (as pressure) for LV filling that coincides with mitral valve closure to opening

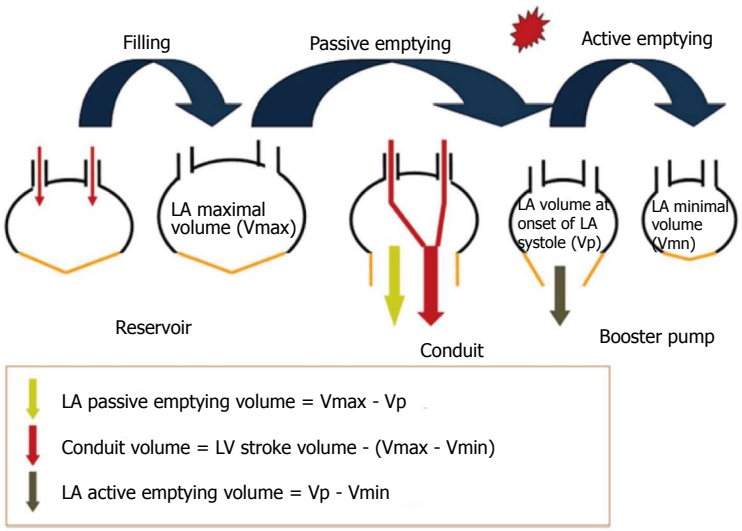

Figure 1 Phases of left atrial function. Left atrial preload is determined by blood flowing from the pulmonary vein. In this initial filling phase the LA acts a reservoir storing blood during left ventricular systole against a closed mitral valve. During LV diastole, diastasis and as the mitral valve opens it acts as a conduit, passively using stored energy to empty into the LV. Finally, in LV end diastole the LA contracts and actively empties blood completing the LV filling cycle. Reprinted from Karayannis *et al*[21], with permission of the publisher (Copyright © 2007, Springer Science + Business Media. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation). LA: Left atrial; LV: Left ventricle; Vp: Left atrial volume before atrial contraction; Vmax: Maximal volume (as defined at left ventricular end-systolic phase); Vmin: Left atrial minimal volume (as defined at left ventricular end-diastolic phase).

and ventricular events of isovolumic contraction, ejection and isovolumic relaxation; (2) a conduit (phase) for transiting blood (in early diastole) from the pulmonary veins to the LV after a pressure gradient develops to open the mitral valve and also passively during diastasis and is dependent on LV relaxation and preload; (3) a pump (contractile phase) to provide a "booster" depending on the preload, afterload, intrinsic contractility and electromechanical coupling [term defines the time between atrial electrical activation and mechanical activation (19)] to augment LV filling in late diastole; and (4) a suction effect to refill itself in early systole.

The LA contributes upto 30% of LV filling (The three phases can contribute around 40%, 35% and 25% respectively). LA flow from the pulmonary veins is continuous while LV filling is intermittent. The LA also acts as a volume sensor and regulates fluid balance by, neurohormonal function with production and regulation of natriuretic peptides, by regulatory (barometer) function *via* mechanoreceptors, and by interaction with renin angiotension aldosterone system/pathway (RAAS)[19-25].

LV and diastole

LV diastole coincides with LA systolic phase. Of the four parameters used to define diastolic function, three, LV relaxation, distensibility (restoring force) and stiffness (compliance) are predominately determined by LV characteristics and morphology. The fourth, LV filling or preload has significant LA contribution and is a compensation to maintain stroke volume (SV). Through LA and LV preload, afterload, contractility and electromechanical coupling passive and active atrioventricular connectivity are established. There are several publications that describe and evaluate LV aspects of DHF are cited[1,3,12,13,19,26,27]. Diastole is described in four phases and these phases can be related to phasic LA events (Figure 2)[28]: (1) Isovolumic relaxation during LA reservoir period; (2) rapid early filling; (3) diastasis during LA conduit phase; and (4) late filling, during atrial contraction phase.

Left atrial remodelling

When there is pressure and volume overload the process of atrial remodeling starts. In 220 healthy patients, age related LA indexed volumes changed only beyond the eight-decade[29]. In contrast, and without increasing LA size, changes in phasic atrial volumes and augmentation of LA contraction occur earlier, corresponding with age related alterations in LV diastolic relaxation[30,31]. Changes in the indexed LA volume (LAVi) appear to parallel the grade of diastolic diastolic dysfunction (DD)[22]. Atrial arrhythmias is an independent precipitant of atrial remodeling. The response of atrial cell to external stress incites hypertrophy, fibrosis and subsequently LA dilatation and hypocontractility[21]. LA dysfunction may alter the reservoir and conduit functions of the atrium and reduce the ability to absorb increases in LVEDP being transmitted to the pulmonary vasculature, for which there is a threshold similar to LV Frank-Starling mechanics[32]. Loss of phasic LA pump function can also lead to symptoms by reducing late LV diastolic filling, which is more marked when there is preexisting systolic impairment[25,33]. Pressure load to the LA can be seen in mitral stenosis and or increased LVEDP. Volume loading occurs in mitral regurgitation, intracardiac shunts or arteriovenous fistulae and high cardiac output states. These have to be factored in using LA metric when

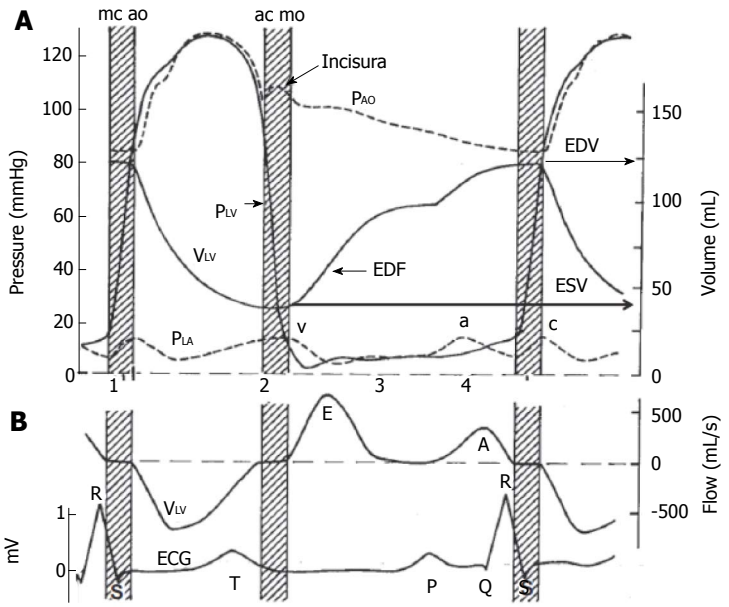

Figure 2 Describes the volume and flow relationships in the left atrium and left ventricle throughout one cardiac cycle, *i.e.*, systole and diastole. A: Pressure (P) and volume (V) are presented for the Aorta (Ao), left atrium (LA) and left ventricle (LV). Systole: During the early phase between mitral valve closure (mc) and aortic valve opening (ao) is the isovolumic contraction phase (stripped bar), where there is increase in PLV (solid line) without change in VLV (solid line). This is followed by ventricular contraction with a rise in PLV and PAO (upper dashed line), that peaks mid cycle, and a reduction in VLV. Diastole: At the end of LV contraction, and when the PLV is lower than the aorta the aortic valve closes (ac), followed by a period of isovolumic LV relaxation (stripped bar), where there is reduction in PLV without a change in VLV. The Incisura or dicrotic notch describes the small backflow of blood into the LV. Early diastolic point of early diastolic filling. In diastole PLA is generated early by the reservoir and conduit atrial function (v wave - lower dashed line) and corresponds with early diastolic filling (EDF) and a late atrial contraction or booster function (a wave) and contributes to late diastolic filling. Ventricular volumes are as end diastolic or end systolic (EDV or ESV; solid line). Cardiac sounds are shown as 1-4; B: Diagram showing relationship between electrical conduction and blood flow with an additional catheter in the LV. Systolic blood flow out of the ventricle (V LV), is followed by early diastolic blood flow into the LV (E wave), bate blood flow into the LV during LA contraction (A wave). A standard ECG lead II shows LA depolarization, LV depolarization, and LV repolarization (P wave, QRS complex, and T wave, respectively) (Published in Ref 28, figure provided courtesy of Dr. John V. Tyberg and Dr. Henk E. D. J. ter Keurs. Permission required). ECG: Electrocardiogram.

evaluating DD.

ROLE OF ATRIUM IN DHF WORKUP

In a patient with SOB, echocardiography will firstly confirm LV systolic function (*i.e.,* normal or mildly impaired ventricle (LVEF > 50%). A body of evidence is developing however to suggest that "sub clinical" systolic dysfunction such as reduced longitudinal LV shortening are present, and occur before the alteration seen in LVEF. At this stage the clinical context for DHF is evolving. Cardiac imaging with echocardiography however does not directly measure LVEDP and infers this by changes in volume, blood and tissue velocities. Invasive measures (LV pressure tracing or pressure volume data) and natriuretic peptides can provide direct information on myocardial stretch and hence diastolic abnormalities[15]. However, the noninvasively evaluated e/e' (ratio of early diastolic transmitral velocity to early diastolic tissue velocity) serves as a surrogate of LV EDP.

Some patients manifest symptoms during exercise and this similarly can be assessed[27,34-37]. There is no single non-invasive index that confirms or rules out the diagnosis, however using a combination of parameters, this can be achieved (Figure 3). Furthermore it is unclear if any one parameter provides greater weight than another.

Left atrium as a biomarker

There is a volume of data to support LA enlargement and adverse cardiovascular outcomes independent of age, gender and the major comorbid cardiovascular risk factors[22,38,39]. In fact LA dilatation should be considered pathological before the eight decade[28]. Among 2042 residents in Olmstead County, Minnesota over 45 years of age, LAVi predicted all cause mortality, as did the grade of DD[40]. From the same community, retrospective analysis of 1160 participants (> 65 years) followed for 3.8 ± 2.7 years, LAVi > 32 mL/m^2 predicted risk for first cardiovascular event (P = 0.003)[41]. Several studies with 851 and 1495 patients over 65 years of age, found that measures of LA size predicted new development of HF[42,43]. This risk was also demonstrated in 483 younger participants (mean age 47 years) followed for 6.8 years, where Leung *et al* showed that LAVi > 24 mL/m^2 was the only independent echocardiographic predictor of cardiovascular death, congestive heart failure, myocardial infarction, stroke and atrial fibrillation. Using a variety of methods, studies show an increase in cardiac and all cause mortality in a general population[44,45], following myocardial infarction[46,47], and with dilated cardiomyopathy[48]; predicts ischemic heart disease[41,49,50], atrial fibrillation and stroke[40,41,44,49-56].

Alteration in LA mechanics (function), with or without LA dilatation, correlate with disease states such as

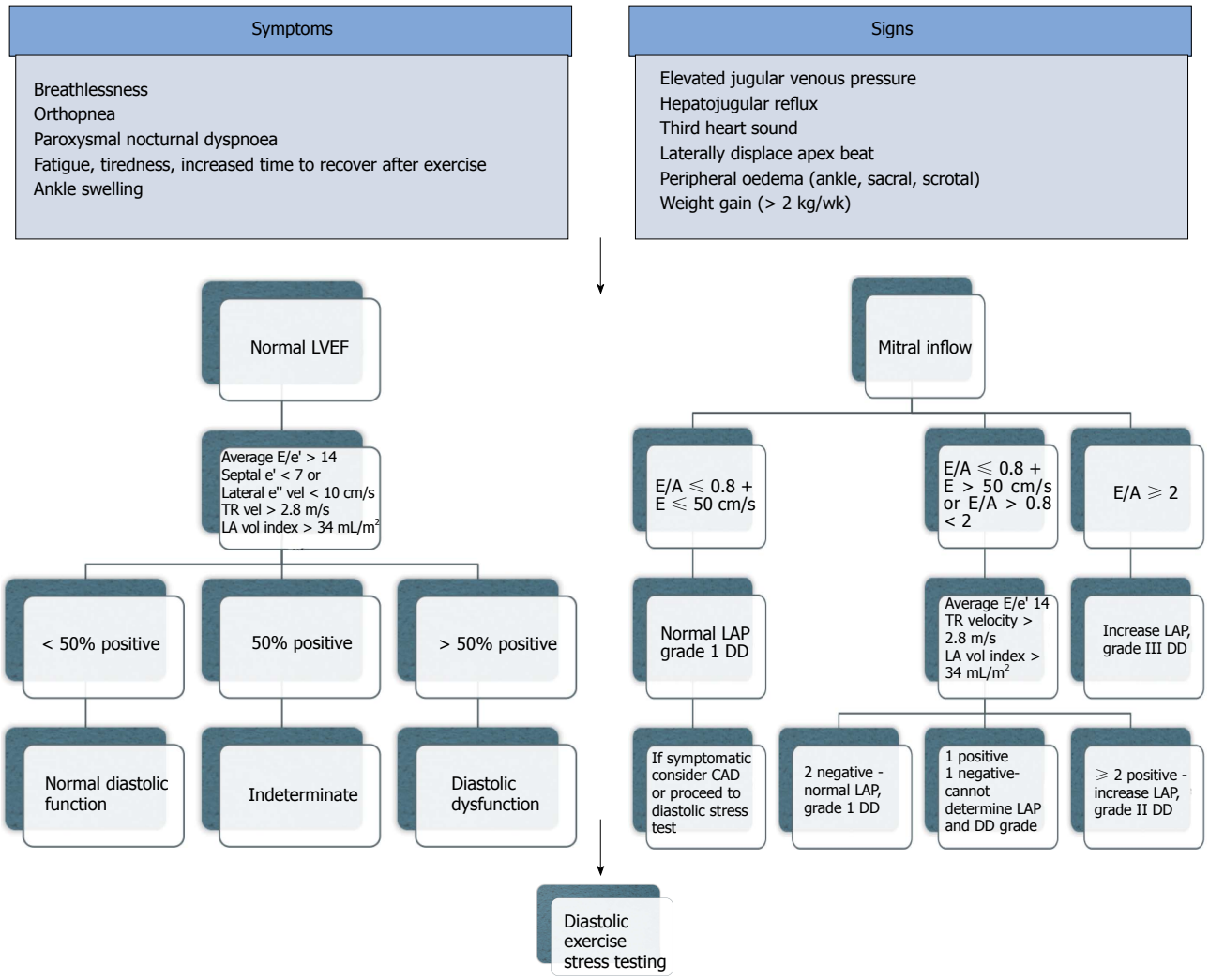

Figure 3 How to diagnose heart failure with preserved ejection fraction. From the 2016 consensus statements of HF, the diagnosis of HF requires 4 important factors: (1) the presence of symptoms and/or signs of HF; (2) a "preserved" EF (defined as LVEF ≥ 50% or 40%-49% for HfmrEF; (3) elevated levels of natriuretic peptides (BNP > 35 pg/mL and/or NT-proBNP > 125 pg/mL); (4) objective evidence of other cardiac functional and structural alterations underlying HF; and (5) In case of uncertainty, a stress test or invasively measured elevated LV filling pressure may be needed to confirm the diagnosis. However in clinical practice many patients present predominately with a symptom such as SOB. The new guidelines are a positive step forward, and the authors for the first time acknowledged LA size, a surrogate for chronically elevated LVEDP and LA dysfunction. They fall short however as there are confounders for the abnormalities and none of the factors can be conclusively correlated to symptoms, where exercise testing could. A: Atrial filling velocity; BNP: Brain natriuretic peptides; E: Early filling velocity; e': Early mitral annular tissue doppler velocity; EF: Ejection fraction; HfmrEF: Heart failure mid-range ejection fraction; LA: Left atrium; LAP: Left atrial pressure; LV: Left ventricle; LVEDP: Left ventricular end diastolic pressure; NT-proBNP: N Terminal Brain Natriuretic peptide; TR: Tricuspid regurgitation (adapted from References 1 and 3).

hypertension, diabetes and renal impairment, and to adverse outcomes[57,58]. In 1802 participants of the Dallas Heart study imaged with magnetic resonance imaging, decreasing LA emptying fraction was independently associated with mortality but not LAVi[59]. In HF the reservoir and conduit functions are inversely related with Doppler parameters of DD and LVEDP. As HF progresses atrial contractility also gradually declines[60-62]. Early changes in LA mechanics, correlations with comorbidities and disease severity and recovery with treatments, have been demonstrated for hypertension[63-65], atrial fibrillation[66-70] and valvular heart disease, using a variety of methods[19,22].

Left atrium as a barometer

LA changes particularly the LAVi reflects the chronicity and cumulative effects of changes in LV filling pressures. While the LAVi does not reflect acute changes in LV pressures it can be used as a barometer for chronically elevated LV filling pressures. This change can persist for some time after pressures have normalized. Increased LA volume can also be seen in athletes, bradycardia, anemia, high output states, atrial arrhythmias and mitral valve disease, independent of diastolic dysfunction. When these conditions are excluded LAVi > 34 mL/m^2 should alert treating physicians to the possibility of DD and raised LV filling pressures[15].

To summarize the data, firstly LA size is a marker of health in a population; secondly a change in size highlights a remodeling process that predicts adverse outcomes; and thirdly alterations in LA size and mechanics potentially is caused by alterations in LV

diastolic filling abnormalities due to atrioventricular interdependence[40].

IMAGING THE LEFT ATRIUM

Conventional echocardiography is sufficient to assess atrial size, but a combination of conventional and novel techniques are required to assess atrial mechanical functions.

Left atrial size assessment

M-mode and 2D echocardiography measuring the antero-posterior diameter, as performed in early studies, is now agreed to be an inadequate measure of LA size. Both the American and European Society of Echocardiography are in consensus that LAV using either the ellipsoid model or Simpson's method in two and four chamber apical views is more accurate as LA enlargement occurs asymmetrically. When the LAV is indexed (LAVi) it provides the strongest association, most sensitive predictor and risk stratification tool for cardiovascular outcomes[2,3,22,38]. A detailed description of LAV is highlighted below[55].

LA passive volumes consist of: (1) Preatrial contraction volume (V_{preA}), measured at the onset of the P-wave on an electrocardiogram (ECG); (2) minimal LA volume (V_{min}), measured at the closure of the mitral valve in end-diastole; and (3) maximal LA volume (V_{max}), measured just before the opening of the mitral valve in end-systole.

LA active volumes are: (1) LA reservoir volume (V_{max} - V_{min}); (2) LA conduit volume (LV total SV - LA reservoir volume); (3) LA passive emptying volume (V_{max} - V_{preA}); and (4) LA contractile volume (V_{preA} - V_{min}).

Physiological associations of LA size have been noted with body size and gender, but these differences are not apparent once indexed to BSA. Age related changes are seen at the extremes but not with normal aging. Based on the sensitivity and specificity for predicting cardiac events, population studies have shown mean LAVi by biplane Simpsons or area length method was between 20-23 ± 6-7 mL/m^2, giving a normal value of 22 ± 6 mL/m^2[31,40,44,51,53]. In the guidelines, 1 standard deviation (SD) from the mean > 28 mL/m^2 is considered LA enlargement and 2 SD from the mean > 34 mL/m^2 for DD[3,18,21]. Pressure load to the LA can be seen in mitral stenosis and or increased LVEDP. Volume loading occurs in mitral regurgitation, intracardiac shunts or arteriovenous fistulae and high cardiac output states. These have to be factored in evaluating DD and LA changes. Factoring these conditions LAVi has been shown to strongly correlate with the degree of DD and even differentiate between normal and pseudonormal filling patterns[19,20,22,50,71,72].

Left atrial function assessment

The gold standard test atrial volume loop is invasive and not routinely available. Four established echocardiographic parameters can provide information on the varying phases of LA function with advantages and disadvantages (Table 1).

2D volumetric analysis (the volume method) is the simplest but requires skill in obtaining the images and is time consuming. It uses LA volume at their maximum, minimum and just before LA systole to determine function.

Spectral (pulsed wave) Doppler of transmitral flow and pulmonary veins (sampled at mitral leaflet tips) are readily available, easy to use but only provides estimate of LA function. It is dependent on immediate loading conditions and can be affected by myocardial tethering acquisition angle, heart rates, atrial fibrillation, conduction system disease, age related reductions in LV diastolic compliance, altered hemodynamics and mitral valve disease. Peak transmitral A wave velocity, velocity time integral and atrial fraction can be used to measure LA contractile function and has been beneficial in following correction of atrial fibrillation with cardioversion, cathether ablation or surgery[53,71-78]. The atrial ejection force can be calculated with several assumptions of the density of blood and a circular mitral annulus area, where diameter is measured in 4-chamber view. This has found correlation with return of atrial function post cardioversion, adverse cardiovascular remodeling and cardiovascular events[79,80], although significant technical limitations persist[20]. Importantly all Doppler measurements can only be performed in sinus rhythm.

Tissue Doppler imaging of intrinsic myocardial velocity (*e.g.,* mitral annulus), can provide regional and when averaged from several sites, global function. It is a low-velocity and high amplitude signal and has the advantage of being load independent. Tissue Doppler has deficiencies of angle dependency (acquisition angle - long axis), is dependent on cardiac motion and myocardial properties such as tethering and annular sampling site. A' values has been shown to be a useful surrogate of global LA function, while all parameters (S', E' and A') provide useful prognostic information[20,31,81-86].

Deformation analysis with strain and the speed of deformation with strain rate imaging can quantify regional and global function independent of tethering. Values however show regional variation[63,73]. Positive values are seen with chamber dilatation and wall stretch and negative values with contraction. Similarly this method has shown correlations with clinical outcomes and prognosis such as maintenance of sinus rhythm and atrial mechanics in atrial fibrillation[67-71,87], New York Heart Association Functional Class[97], LA contractile function[63,65], hypertensive heart disease[64,66] and valvular heart disease[19].

EXERCISE DIASTOLOGY

SOB and exercise intolerance due to HFpEF, should demonstrate an increased LVEDP with exercise. The

Table 1 Imaging modalities and their correlations with components of atrial function[1]

LA function	Volumetric	Spectral Doppler			Tissue Doppler and deformation indexes		
	LA volume fraction	Transmitral flow	PV flow	Composite indexes	TDI	Strain (ε)	Strain rate
Global	LA EF [(LAmax - LAmin)/LAmax]	-	-	LAFI	-	-	-
Reservoir	Expansion index [(LAmax - LAmin)/LAmin]	-	S	-	S′	S; total	S
Conduit	Passive EF [(LAmax - LApre-A)/LAmax]	E E/A	D	-	E′	e-pos	E
Contractile (Booster)	Active EF [(LApre-A - LAmin)/LApre-A]	A E/A AFF	PVa	Ejection force (AEF) LAKE	A′	a-neg	A

[1]Table modified from Ref[20,22]. ε: Strain; A/A′: Atrial contraction velocity/tissue Doppler velocity; AEF: Atrial ejection force Atrial ejection force = 0.5 × 1.06 g/cm3 × mitral annulus area (peak A velocity). Mass of blood is calculated as the product of the density of blood (ρ = 1.06 g/cm3) and volume of blood passing through mitral annulus; AFF: Atrial filling fraction, the ratio of the velocity time integral of the mitral A wave to the total diastolic transmitral flow; E/E′: Early diastole velocity/tissue Doppler velocity; EF: Emptying fraction; LA: Left atrial; LAEF: Left atrial emptying fraction; LAFI: Left atrial functional index; LAKE: Left atrial kinetic energy; LAmax: Maximum left atrial volume; LAmin: Minimum left atrial volume; neg: Negative; pos: Positive; preA: Preatrial contraction; PV: Pulmonary venous; Pva: Pulmonary venous reversal velocity; S/S′: Ventricular systole velocity/tissue Doppler velocity; TDI: Tissue Doppler imaging.

proven exercise protocols are stress echocardiography, combined stress echocardiography and cardiopulmonary stress test, and right heart catheterization with exercise[27,34-36,88-98]. HFpEF is a systemic condition with an interaction of the primary cause coupled with secondary pathophysiological changes in the LV and LA. The continuity of the vasculature places the cardiac and peripheral endothelial beds at risk of injury when chronically exposed to risk factors. This loss of compliance or efficiency can see disproportionate rises in LV filing pressures, which can be buffered for, *e.g.,* by changes in atrial function[27]. Thus a combination of deficits in arterial-ventricular-atrial function will be present in symptomatic individuals where a rise in LVEDP or LA pressure is the common denominator.

Burgess *et al*[91] studied 37 patients at baseline and after supine cycle ergometry, and found that the e/e′ of > 13 correlates with an elevated LVEDP during exercise. In another 166 patients post-exercise e/e′ > 13 was highly specific (90%) for stratifying an exercise capacity of < 8 METs or > 8 METs[91]. Nedeljkovic *et al*[89] studied 87 patients with HTN, exertional SOB and normal resting LV function with combined exercise stress echocardiography cardiopulmonary testing to identify masked HFpEF found correlations between e/e′ > 15 and reduced peak V02 and other parameters with high sensitivity and specificity. Maeder *et al*[36] identified 14 patients with diagnosed HFpEF and matched controls, who subsequently underwent supine cycle ergometer exercise, found that patients with HFpEF achieved a similar pulmonary capillary wedge pressure (PCWP) to asymptomatic controls at a much lower workload. However, contrary to Burgess *et al*[91], the e/e′ did not reflect the hemodynamic changes during exercise in HFNEF patients.

Pulmonary artery pressures, which can act as a surrogate for elevated left sided filling pressures can also be used. This spectral Doppler method measures the tricuspid regurgitation (TR) jet velocity and applies the formula $4V^2$ + right atrial pressure (V = Doppler velocity of regurgitant jet). Standardized measures of right atrial pressure are readily available from guideline and textbooks. While the non-invasive stress test is practical and translatable, translational gaps persists partly due discrepancies in role of e:e′ found in Burgess *et al*[91] and Maeder *et al*[36], identifying a suitable adjunct for pulmonary artery pressures when TR is absent, and establishing values that constitute elevated pressures across the spectrum of resting diastolic profiles, and baseline pulmonary artery pressures.

RATIONALE AND ARGUMENTS FOR FUTURE CLINICAL STUDIES OF DHF

Clinical correlation of atrial derived parameters

The current understanding of diastology does not allow us to definitively correlate symptoms to the varying changes in diastolic profiles. In addition no single parameter can be used to determine the diagnoses. In the process of grading diastolic abnormalities changes in the mitral valve velocity profiles and tissue Doppler occur as a normal part of aging. With the advent of exercise diastology and the inclusion of left atrial volume in the most recent guidelines, highlights the importance of looking for evidence that LV filling pressures are elevated in a patient with SOB. We thus feel that an important first step is to document an increase in intracardiac pressures and the subsequent steps should go on to explore the causes for this both in the LV and LA. The bases for the later is that many of the atrial derived parameters are used to define LV diastolic function, with little emphasis on how changes in LA function could alter this.

Terminology

DHF syndrome is a broad categorisation of a complex syndrome with multiple contributors where the end result is SOB and clinical impairment. Unlike SHF where the entirety of the syndrome is coupled with an impairment of LV myocardial contractility, in HFpEF it remains unclear how the interplay between degrees of LV stiffness and LA dynamics contributes to symptoms. Thus terminology in HFpEF should reflect the atrioventricular interaction in LV diastole. Lets explore several hypothetical case examples: (1) HfpEF - With predominantly impaired LV relaxation. In this scenario a patient would have clinical symptoms and signs, abnormal LV diastolic parameters, has demonstrated elevation of LVEDP (at rest or exercise), without significant LA abnormalities, and a shift of LVEDP and volume curve to the left; and (2) HFpEF - secondary to atrial dysfunction/atrial fibrillation. In this scenario the patients have similar presentation as above, however despite rate control, remains symptomatic. Restoration of sinus rhythm correlates with clinical improvement of symptoms.

Part of establishing the terminology requires an improved understanding of all aspects of LV and LA abnormalities.

Future clinical studies

The premise of any future study should be based on consolidating the diagnosis with this point in mind: "In a patient with SOB and normal LVEF the diagnosis of HFpEF can only be consolidated by reproducibly demonstrating an elevation of LVEDP or LA pressure before treatment, that this elevation is outside a physiological norm and correlates with the patients symptoms". The premise of therapeutic studies while not the aim of this paper should also focus on atrioventricular pathophysiological derangements. From this point we can explore the steps in cardiac investigations.

Screening: (1) Firstly all patients should have a screening echocardiogram; and (2) epidemiology studies are still needed to correlate the chronology of diastolic parameters with time and symptoms.

Demonstrating increased LVEDP: Firstly, we need to demonstrate an increase in LVEDP, and secondly we need to demonstrate the abnormality in the atrioventricular context. An important question then is should exercise stress testing be a routine part of DHF work-up? Due to cost, availability and the sheer volume of patients' invasive tests seem unrealistic, however non-invasive exercise echocardiography could screen patients needing an invasive test. Secondly, what parameters to use? (1) Pulmonary artery pressure elevations detected by exercise stress echocardiography can be a surrogate for LVEDP. Excluding other causes for pulmonary hypertension is important. When TR is absent patients could go onto an invasive exercise right heart study; and (2) The role of e/e' and other variations in spectral and tissue Doppler parameters requires further attention. There is conflicting data from studies in the former and a lack of data for the latter[36,99]. Thirdly, natriuretic peptides: Are secreted in response to atrial (atrial natriuretic peptides) or ventricular (brain natriuretic peptides) stretch. These factors have different biological properties such as chamber secreted and half-life can be exploited for diagnosis and monitoring. In clinical translation its utility with exercise stress echocardiography as a surrogate for an invasive right heart study derived LVEDP is yet to be defined[95].

Atrial function: Is difficult to assess both at baseline and with exercise, as there are no clinically friendly tools. As many of the echocardiographic derived DHF parameters correlate with atrial mechanics, understanding how these parameters change with LA disease will better inform LV diastology. Several examples: From an invasive study in dogs undergoing exercise, it is observed that reservoir and booster functions increase but not conduit function[96]; in 50 HFpEF patients, using late diastolic mitral annular velocity and calculated left atrial reserve index, found reduced LA function with exercise that could contribute to symptoms in addition to LV systolic and diastolic abnormalities[97]. An improved understanding could also help inform future therapies targeting the LA.

Reliability in monitoring: Issues that need to be addressed are inter and intraobserver variability and the correlation of diastolic parameters following treatment and with changes in clinical status over time[100].

Diastolic compensation and chronology: For patients who have abnormal baseline diastology who do not demonstrate increases in LVEDP with exercise, we will need to find satisfactory means to exclude HFpEF from the diagnosis. This will require improved understanding of diastolic compensation in the chronology of myocardial cellular function, where a different result could be elicited with different conditions.

CONCLUSION

SOB is a common symptom presentation to cardiology clinics. Clinical workup can point toward coronary artery disease, HFrEF, respiratory causes or anemia. There is also a sizable group where differentiation is required between deconditioning, obesity or HFpEF. Thus diagnosis of HFpEF has and still remains difficult where no one parameter we have is "a smoking gun". Baseline echocardiographic parameters have translated into flow diagrams published in the latest guidelines. There remain however important gaps in the understanding of this syndrome: (1) Diastolic function is complex in that it requires functional mechanics of both the atrium and ventricle, where less importance has been placed in understanding LA function; (2) exercise stress echocardiography is underutilized in the diagnostic

work-up; (3) our understanding of the baseline and subsequent parameters in its reproducibility and clinical translation requires more study; (4) the terminology defining the major contributor to HFpEF into atrial or ventricular dysfunction, should be explored; and (5) the translation of diagnostic findings into the clinical context such as relieving LVEDP, addressing myocardial stiffness with antifibrotics, correcting or augmenting atrial function and perhaps even devices to improve atrioventricular electrical or mechanical functions. To satisfactorily deliver optimal treatments more studies are needed to consolidate on our understanding and to confidently provide the diagnosis of HFpEF in a patient presenting with SOB.

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REVIEW

Is forced oscillation technique the next respiratory function test of choice in childhood asthma

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Abstract

Respiratory diseases, especially asthma, are common in children. While spirometry contributes to asthma diagnosis and management in older children, it has a limited role in younger children whom are often unable to perform forced expiratory manoeuvre. The development of novel diagnostic methods which require minimal effort, such as forced oscillation technique (FOT) is, therefore, a welcome and promising addition. FOT involves applying external, small amplitude oscillations to the respiratory system during tidal breathing. Therefore, it requires minimal effort and cooperation. The FOT has the potential to facilitate asthma diagnosis and management in pre-school children by faciliting the objective measurement of baseline lung function and airway reactivity in children unable to successfully perform spirometry. Traditionally the use of FOT was limited to specialised centres. However, the availability of commercial equipment resulted in its use both in research and in clinical practice. In this article, we review the available literature on the use of FOT in childhood asthma. The technical aspects of FOT are described followed by a discussion of its practical aspects in the clinical field including the measurement of baseline lung function and associated reference ranges, bronchodilator responsiveness and bronchial hyperresponsiveness. We also highlight the difficulties and limitations that might be encountered and future research directions.

Key words: Asthma; Forced oscillation technique; Impulse oscillatory; Pre-school; Children; Pulmonary function test

Core tip: Respiratory diseases, such as asthma, are especially common in children. Although their diagnosis and management are facilitated by using spirometry in older children, the use of the latter remains limited in younger children because of their inability to perform forced expiratory manoeuvre. Therefore, the use of new methods which require minimal effort and cooperation from children, such as the forced oscillation technique (FOT) is a welcome and promising addition to identify children with underlying airway function abnormalities. In this article, we review the available literature on the use of FOT in childhood asthma.

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INTRODUCTION

Asthma is the most common chronic childhood disease worldwide[1]. It is often difficult to diagnose in infants and young children due to lack of objective measures, such as spirometry[2-4].

Spirometry is the gold standard method to assess lung function in older children and adults. However, obtaining acceptable and repeatable spirometry measures requires significant efforts and high level of cooperation[5-7]. Therefore, the diagnosis and management of childhood asthma remain suboptimal, in young children and older children who cannot perform an acceptable forced expiratory manoeuver.

One potential lung function method suitable for use in young children and older children unable to perform spirometry is the forced oscillation technique (FOT). The FOT was developed by DuBois *et al*[8] in 1956, to measure the mechanical behaviour of the respiratory system. Over the years, the FOT has been used in research and more recently in clinical practice[9-12]. The application of FOT has expanded to the point where commercial equipment are now widely available. Standardized approaches for the collection of FOT outcomes have been established by the European Respiratory Society (ERS) and the American Thoracic Society (ATS) in pre-school children[9].

One significant advantage of the FOT is its application during tidal breathing and the subsequent reduction in the level of active participation and cooperation required from the individual being tested. As a result, this technique can be feasibly used in children as young as two years of age[13]. Consequently, the FOT opens new frontiers in the application of objective measurements of respiratory function in young children and offers improvements in the diagnosis and management of asthma in young children.

In this review we have summarised the available literature on the use of FOT in childhood asthma. The technical aspects of FOT are briefly described followed by a discussion of its practical aspects in the clinical field, including the measurement of baseline lung function and associated reference ranges, bronchodilator responsiveness and bronchial hyper-responsiveness. We also highlight the difficulties and limitations that might be encountered and future research directions.

Technical aspects of FOT

The basic principle of FOT involves the application of external signals into the respiratory system and measuring the resulting response of that system[10]. This response is termed the respiratory system impedance (Zrs). The Zrs can be determined when flow and pressure are measured across a known frequency range at the airway opening and is represented as the resistance (Rrs) and reactance (Xrs) of the respiratory system

$$Zrs = Pao / V'ao = Rrs + j\,Xrs$$

where Pao is the pressure V'ao is the flow measured at the airway opening and $j = \sqrt{(-1)}$

Resistance (Rrs) represents the component of Zrs that is a function of both Pao and V'ao, equating to the resistive properties of the respiratory system. Reactance (Xrs) is the out-of-phase component that is a function of both Pao and volume, reflecting elatic recoil of the respiratory system. Both Rrs and Xrs are determined when oscillatory (sound waves) signals are applied at the airway opening (and hence to the whole respiratory system).

It is important to be aware that the respiratory impedance is frequency-dependent: (1) At low frequencies, (2-4 Hz) as the oscillations are transmitted more distally into the lungs, Rrs and Xrs tend to reflect the properties of the peripheral respiratory system; (2) at higher frequencies, (> 20 Hz) the Zrs reflects the resistive and inertive properties of the proximal conducting airways.

It is critical to note that Rrs and Xrs reflect mechanical properties of the entire respiratory system, including the airway, lung and chest wall[10]. It is therefore not possible to assign specific anatomical changes (for example central airway obstruction) to changes in any one FOT outcome at a specific frequency (see below for further details).

As the airway and the lung tissue are both flow and volume-dependant, the characteristic of the oscillatory signals used is important. These signals can take any of the following common forms: (1) Single frequency; (2) impulse oscillation system[14]; (3) pseudorandom noise (the simultaneous application of several frequency components).

The oscillation signal that is most commonly applied encompasses the medium frequency range, generally including frequencies between 2 Hz and 20 Hz. The advantage of using mid-range frequencies is that the oscillatory signals can be superimposed on the tidal breathing and therefore result in a broader application[10]. For more details reviews on the technical aspects of FOT, readers are directed to review (oscillation mechanics of respiratory system) by Bates *et al*[15].

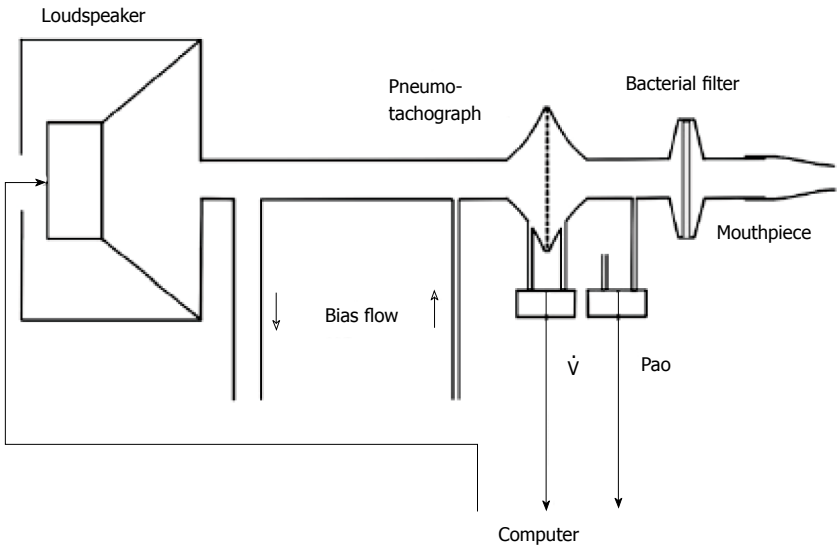

Figure 1 Typical arrangement of the forced oscillatory impedance measurement, adapted from. Pao: Input pressure at the airway opening; V'ao: Output flow.

Practical aspects of FOT

This section summaries the available equipment, feasibility, repeatability, and finally the collection and reporting of FOT data in young children.

Equipment

The availability of FOT commercial equipment has resulted in the increased uptake of FOT in clinical practice and especially in young children. The FOT equipment includes (Figure 1): (1) A loudspeaker or similar to generate the oscillatory signals; (2) a pneumotachograph and pressure transducers to measure pressure and flow; (3) a mouth piece containing a bacterial filter to prevent cross infection between patients**.** A typical arrangement of the forced oscillatory impedance measurement, adapted from[9].

Feasibility

The feasibility and success rates of FOT are, understandably, age-dependent. The success rate in children 4 years of age and older exceeds 80%[13,16,17], while it ranges from 83% to 100% in healthy children aged 2-7 year[13,18] and between 57% to 100% in children with asthma aged between 3 to 5 years[13,16]. In young children with acute asthma the success rate of FOT reduced to 24% and 65% in three and eight-year-old children respectively, However, it was higher than that of spirometry in the same population[12]. Furthermore, the feasibility of FOT measurements increases noticeably with practice in children.

The feasibility of FOT with challenge testing has been assessed in several research studies and has been shown to be feasible in young children using either inhaled adenosine monophosphate (AMP)[19], free running[20], methacholine[21-23], hypertonic saline[21], cold air[24] or mannitol challenge[25].

Collection of FOT data

For adequate collection of the data, the child should be seated with their back straight and their neck either in the neutral position or slightly extended. FOT is usually performed with the mouthpiece which incorporates a bacterial filter and a nose clip-on. A staff member or a parent needs to support the child's cheeks as well as the floor of his mouth, as shown in Figure 2. An acquisition period should cover several breathing cycles, typically lasting 8-16 s. The results, computed as the mean value of the three to five acceptable measurements, also include the measurement of the coefficient of variation calculated from the standard deviation (SD) of the measurements. Acceptable measures are the one which have no artefacts such as leak, incomplete expiration, glottis closure, swallowing and the child obstructing the mouthpiece with their tongue are easily identified[9] (Figure 2).

Repeatability

Repeatability is an important issue when considering the role of a lung function measures. The short-term repeatability of FOT in heathy children has been assessed and it is summarized in Table 1 below. The long term (two weeks) and short term repeatability were both similar[19].

Reporting and interpreting FOT data

Commonly reported FOT outcomes include resistance (Rrs), reactance (Xrs) at different frequencies, resonance frequency (Fres), frequency dependence (Fdep), and the area under reactance curve (AX), as illustrated in Figure 3. The reported Rrs variable includes, in the same measurement, the Rrs of the airway, that of the chest wall, and that of the lung tissue. As airway Rrs dominates Rrs in the mid frequencies[26], it can be considered a surrogate of airway resistance[27,28]. As frequency decreases to below approximately 4 Hz Rrs will increasing include peripheral respiratory resistance and be reflective of the peripheral airways and the lung. As Xrs, on the other hand, is dominated by elastic properties of the respiratory tissue, reflecting the elastic

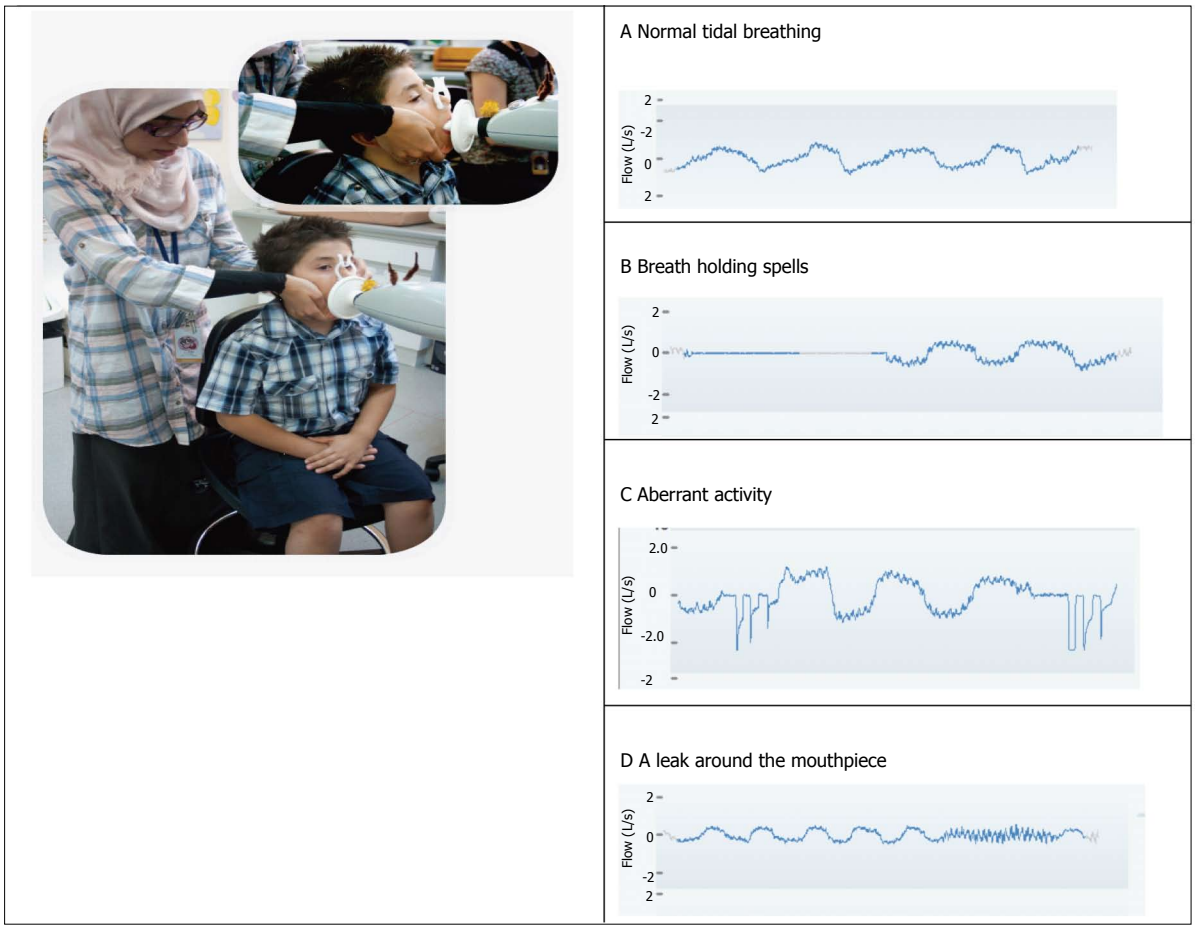

Figure 2 Demonstration of lung function measurements using FOT. On the left, a photograph of the FOT test being performed in a 5-year-old boy. The hands of the investigator support the cheeks and the floor of the mouth of the child. The nose is blocked using a nose clip. The lips are sealed around the mouthpiece. On the right, Different breathing patterns during FOT measurements are shown, as observed on the flow-time trace in L/s. A: Normal tidal breathing; B: Breath holding spells; C: An aberrant activity (*e.g.*, coughing, swallowing, or noise); D: A leak around the mouthpiece. FOT: Forced oscillation technique.

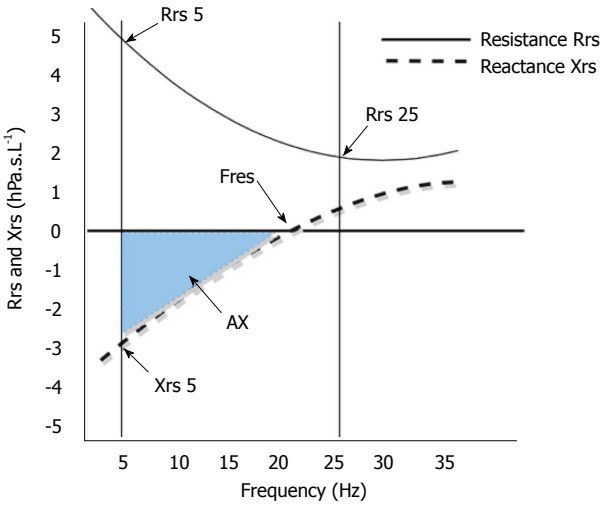

Figure 3 Changes in resistance (Rrs) and reactance (Xrs) as function of oscillation frequency.

and inertive properties of the respiratory system, it is negative at low frequencies. The point at which Xrs crosses the zero, representing the inertial properties of the larger airways[29], is called the Fres, which is the frequency at which elastive and inertive properties of the lung are balanced, and which becomes positive at higher frequencies[30]. The Fdep of that resistance is thought to reflect peripheral airway resistance[31], as, for example, in patients with obstructive airway diseases, it is generally higher than normal subjects due to the difference in airway resistance[30]. However, to date there are no studies directly confirming this.

The area under the reactance curve (AX) is the sum of the Xrs from a Xrs at 5 Hz until Fres (*i.e.*, when Xrs is zero, as in Figure 3)[29]. Studies have shown that Xrs and AX are better representative of peripheral airway obstruction than Rrs[29] and that AX and Fres clearly

Table 1 Fifteen minutes' repeatability of Forced oscillation technique in healthy children

Author	Year	*n*	Rrs	Xrs
Hall *et al*[13]	2007	58; field	~2 or ~ 30%	1.2 - 1.7
Malmberg *et al*[18]	2002	19; placebo	1.1 or ~ 12%	1.3
Klug *et al*[16]	1998	120	2.6 or ~ 20%	2

Rrs: Respiratory system resistance; Xrs: Respiratory system reactance) in hPa/s per L.

Table 2 Populations of healthy children studied using forced oscillation technique since 2005, adopted and modified from

Ref.	Year of publication	Ethnic group - Country of study	Subject number	Age in years	Height (cm)	Reported prediction equation variables
Frei *et al*[35]	2005	Caucasian - Canadian	222	3-10	90-155	Rrs at 5-35 Hz Xrs at 5-35 Hz Fres, AX
Dencker *et al*[36]	2006	Caucasian - Scandinavian	360	2-11	90-162	Rrs at 5-20 Hz Xrs at 5-20 Hz Fres
Amra *et al*[37]	2008	Asian - Iranian	509	5-18	127-197	Rrs at 5-25 Hz Xrs at 5-25 Hz
Nowowiejska *et al*[38]	2008	Caucasian - Polish	626	3-18	95-193	Rrs at 5-35 Hz Xrs at 5-35 Fres
Vu *et al*[39]	2008	Asian - Vietnamese	175	6-11	111-154	Rrs at 8 Hz Xrs at 8 Hz
Vu *et al*[40]	2010	Asian - Vietnamese	95	6-11	111-134	Rrs at 8 Hz Xrs at 8 Hz
Calogero *et al*[41]	2010	Italian	163	2-6	101-114	Rrs at 6-10 Hz Xrs at 6-10 Hz
Park *et al*[42]	2011	Korean	133	3-6	95-121	Rrs at 5, 10 Xrs at 5, 10 RF, AX
Calogero *et al*[43]	2013	Caucasian Italian and Australian	760	2-13	90-160	Rrs at 6, 8, 10 Hz Xrs at 6, 8, 10 Hz Fres, AX
Shackleton *et al*[44]	2013	Mexican	584	3-5	87-119	Rrs at 6 and 8 Hz Xrs at 6 and 8 Hz
Hagiwara *et al*[46]	2014	Japanese	537	6-15	111-174	Rrs at 5 and 20 Hz Rrs5-20

IOS: Impulse oscillation system; Rrs: Respiratory system resistance; Xrs: Respiratory system reactance) in hPa/s per L; Fres: Resonant frequency; RF: Resonant frequency; AX: Area under the Xrs curve from 5 Hz to Fres; MF: Multi-frequency system; Fdep: Frequency dependence of Rrs between 4–24 Hz; SF: Single frequency system.

distinguish healthy children from those with small airway disease and asthma[32].

The FOT outcomes alter with growth and therefore need to be reported as both absolute values and as a function of a predicted value. Expressing outcomes as z or SD scores is the most appropriate. Z scores allows the easy estimation of the lower limit of normal (being either -1.64 or -1.96) and avoids the diagnostic uncertainly that can arise when using percent predicted and a fixed cut off for the presence of abnormal lung function[33,34].

Reference range of FOT measurements

Numerous studies have reported reference data in healthy children using a variety of FOT outcomes[13,35-44]. The FOT outcomes are generally reported to change with age, height and gender. There is some variability due to the different ethnicity, gender, age, weight, height, equipment and the methodology used in those studies and it is important that users carefully review potential reference equations to match the populations, equipment and protocols used as closely as possible to their own circumstances[37,45]. Reporting and comparing the relevant z-scores for these measurements simplifies the interpretation as the possible confounders reported earlier have already been taken into consideration when calculating these scores. Table 2 below summarises those studies and shows those differences.

Clinical applications of FOT in children with asthma

By incorporating measurements of bronchodilator Responsiveness (BDR) and bronchial hyper-responsiveness (BHR), the utility of FOT to assist in the diagnosis of asthma in young children may be increased[47]. The official ATS/ERS statement on pulmonary function testing in preschool children stated that FOT is a promising tool in diagnosing and following up children with asthma[9]. Other studies also suggest that the FOT may be useful in assessing asthma control, compliance to medication, and in the follow up of these young children[48].

Baseline FOT and the severity of asthma

In children aged 5 years and above, spirometry adequately assesses baseline lung function and the results correlate well with asthma severity[49]. When comparing spirometry and FOT in children older than 6 years of age, those with asthma have lower baseline FOT than with spirometry when compared to healthy children[50]. Whilst few studies have examined baseline airway obstruction in young children with asthma using FOT. Klug *et al*[51] reported that young children with stable asthma demonstrated impaired baseline lung function when assessed using FOT. Oostveen *et al*[17] showed that, when compared to healthy 4-year-old children,

those children with persistent wheeze had worse baseline lung function than those with transient wheeze as assessed by FOT. Children with a history of recurrent wheeze and/or asthma recruited from clinics tend to have worse lung function expressed in FOT even when asymptomatic[18,52]. However, other studies conducted in children with history of wheeze and recruited from the community have similar FOT outcomes to healthy children[53,54]. The ability of FOT to determine asthma severity remains therefore questionable, especially in children on asthma medication[49]. Further studies are therefore needed to explore the relationship between baseline lung function using FOT and asthma severity in young children with asthma.

Bronchodilator response using FOT

The assessment of bronchodilator responsivess using FOT in young children with asthma has been encouraged in clinical practice[10]. Critical the the assessment of increased responsiveness associated with asthma is an understanding of the response of healthy children with bronchodilators. The assessment of change in FOT outcomes during the assessment of BDR has been expressed as absolute change or relative change from the baseline in the Rrs, Xrs and AX, the use of AX has been explored in a few studies and is shown to be a good outcome in assessing the BDR in children with asthma[17,29,32].

In the most recent study which assessed BDR in children (Calogero *et al*[43]), cut-offs for a positive BDR in healthy Caucasian children were defined as 34% and 50% for Rrs and Xrs, respectively expressed as a relative change from the baseline lung function. In a study looking at the uses of pseudorandom FOT signal (4–48 Hz) in quantifying BDR in healthy young children, children with cystic fibrosis, neonatal chronic lung disease and children with asthma and/or current wheeze, Thamrin *et al*[53] recommended a positive BD response of 40% and 65% for Rrs and Xrs, respectively expressed as a relative change from the baseline lung function[53]. Another study, conducted by Oostveen *et al*[17] in Belgium on 4 years old healthy and wheezy children (n = 325) using FOT, recommended a positive BDR at Rrs 4 of 43% expressed as absolute changes. Cut-off values for BDR in previous studies are summarized and listed in Table 3. In general, > 30% decrease in Rrs after bronchodilator is suggestive of asthma.

The previous studies in healthy and wheezy young children have not conducted a ROC analysis to formally establish the sensitivity and specificity of a certain BDR cut off to be assessed. Limitations to the wider use of FOT in assessing BDR include the variability of medications, their timing and dosage between the different studies (Table 3).

Bronchial hyper-responsiveness using FOT

Bronchial hyper-responsiveness, usually assessed using spirometry, is the gold standard for confirming a diagnosis of asthma in older children and adults[58,59]. However, false negative or false positive results can occur in young children who cannot perform an acceptable manoeuvre. BHR has been assessed in young children using other methods including FOT, interrupter technique, whole-body plethysmography and transcutaneous oxygen measurement SPO_2[5,47,60-63].

Bronchial hyper-responsiveness studies comparing FOT with different lung function measures have reported FOT to be as effective as spirometry[63-69] and as sensitive as body plethysmography[70] and transcutaneous PO_2[50] in older children with asthma. BHR has been assessed using FOT in children younger than 7 years of age with a range of challenge tests including adenosine monophosphate (AMP)[19], cold air[24], normal saline[21] methacholine[22,62,63,66,68,71], mannitol[25] and exercise[20,72] demonstrating that FOT can be reliably used in young children for challenge testing.

FOT characterization of BHR has been shown to be correlated to asthma severity[73] and to be sensitive to the response to immune therapy[74]. Another study has shown that cough variant asthma showed less BHR in comparison to classical asthma children[75].

Despite the above studies have clearly demonstrated the use of FOT to assess BHR in children, there are few studies demonstrating the best cut off value of BHR between healthy and children with asthma using FOT. Further work is needed before establishing FOT use as clinical tool to assess BHR in children.

Limitation of FOT in children and future direction

Although forced oscillation technique can contribute to the diagnosis and management of childhood asthma, it has some limitations. Although, unlike spirometry, it does not require forced expiratory manoeuvres, it still require some cooperation by children to achieve successful repeatable measures. It is therefore both age and cooperation dependant. The practical advantage of the availability and affordability of different FOT commercial equipment, the Rrs and Xrs output are not always measured at the same frequencies by all these devices. This makes the comparison between different studies challenging. The standardization of the available commercial equipment is therefore still needed and FOT guidelines are currently being reviewed by the ATS and ERS.

As the available FOT reference equations have been constructed in specific populations, these findings cannot be generalised to other ethnic groups. Further studies are therefore still required to establish FOT reference values in other populations or ethnic groups. The assessment of BDR using FOT is not widely implemented because of differences amongst the relevant studies, including differences in the medications used, as well as their timing and dosage. Further studies are therefore required to establish an international standard protocol for this assessment as currently BDR still has not been studied in relation to recent symptoms in young children with wheeze, developing such studies

Table 3 Reported bronchodilator responsiveness in young healthy and wheezy children using forced oscillation technique since 2005

Ref.	Ethnic group age, yr	*n*	Variable	Dose	Waiting time (*n*)	Absolute BDR	Relative BDR, (%)
Thamrin *et al*[53], 2007	Healthy Caucasian (3-7)	78	Rrs 6,8,10 Xrs 6,8,10	Salbutamol 600 mg	15	Rrs 6 -35.0, -3.1 Rrs 8 -35.0, -4.4 Rrs 10 -32.3, -3.7 Xrs 6 -0.27, 1.66 Xrs 8 - 0.04, 1.82 Xrs 10 -0.00, 2.03	Rrs 6: 42% Rrs 8: 37% Rrs 10: 39% Xrs 6: 61% Xrs 8: 67% Xrs 10: 63%
Thamrin *et al*[53], 2007	Asthmatics Caucasian (3-7)	57	Rrs 6, 8, 10 Xrs 6, 8, 10	Salbutamol 600 μg	15	Rrs 6 -37.0, 8.8 Rrs8 -33.1, 9.7 Rrs 10 -33.4, 4.5 Xrs 6 -0.21, 2.30 Xrs 8 -0.13, 2.47 Xrs 10 -0.12, 2.22	Rrs 6: 42% Rrs 8: 37% Rrs 10: 39% Xrs 6: 61% Xrs 8: 67% Xrs 10: 63%
Lan Vu *et al*[39], 2008	Healthy Vietnamese (6–11)	175	Rrs 8 Hz Xrs 8 Hz	Salbutamol 200 μg	5	Rrs 8 -11.8,13.4 Xrs 8 4.09, - 5.78	Rrs 8: 38% Xrs 8: 16%
Lan Vu *et al*[40], 2010	Asthmatic Vietnamese (6-10)	103	Rrs 8 Hz Xrs 8 Hz	Salbutamol 200 μg	5	--	Rrs 8: 13% Xrs: 32%
Oostveen *et al*[55], 2010	Asthmatic Belgian -4	313	Rrs 4	Salbutamol 200 μg	15	--	Rrs 4: 22% AX: 15.77%
Calogero *et al*[41], 2010	Healthy Italian (3-6)	163	Rrs 8 Xrs8	Salbutamol 200 μg	15	--	Rrs 8: 35% Xrs 8: 34%-61%
LEE *et al*[57], 2012	Healthy Korean	161	Rrs 5, 10, 15, 20, 25, 35 Xrs 5, 10, 15, 20, 25, 35	Salbutamol 200 μg	15	Rrs 5 -0.127 Rrs 10 -0.098 Rrs 15 -0.073 Rrs 20 -0.056 Rrs 25 -0.056 Rrs 35 -0.057 Xrs 5 0.062 Xrs 10 0.057 Xrs 15 0.059 Xrs 20 0.044 Xrs 25 0.033 Xrs 35 0.054 Fres -2.167	Rrs 5: 11.8 Rrs 10: 10.8 Rrs 15: 8.7 Rrs 20: 6.972 Rrs 25: 7.029 Rrs 35: 6.095 Xrs 5: 13.474 Xrs 10: 25.946 Fres: 10.457
Calogero *et al*[43], 2013	Healthy Australian and Italian (2-16)	502	Rrs 6, 8, 10 Xrs 6, 8, 10 Fres, AX	Salbutamol 200 μg	15	Rrs 6 -2.9 Rrs 8 -2.74 Rrs 10 -2.39 Xrs 6 -1.80 Xrs 8 - 1.93 Xrs 10 -1.90 AX -33 Fres -12	Rrs 6: 34 Rrs 8: 32 Rrs 10: 31 Xrs 6: 50 Xrs 8: 65 Xrs 10: 74 AX: 81 Fres: 47

BDR: Bronchodilator responsiveness; Rrs: Respiratory system resistance; Xrs: Respiratory system reactance in hPa/s per L; Fres: Resonant frequency; AX: Area under the Xrs curve from 5 Hz to Fres; MF: Multi-frequency system; Fdep: Frequency dependence of Rrs between 4-24 Hz.

would help not only in the follow up of children with wheeze, but also to ascertain the level of control of asthma symptoms and the compliance to medication in children with asthma.

Further research is also required to assess BHR, particularly in young children, in addition to standardise the use of FOT in young children for BHR assessment.

Recently there are new studies that have reported Rrs or Xrs from either expiration or inspiration (or both), including flow limitation within a breath. Those studies suggest that this approach is more sensitive than standard reporting of FOT. However, significant work is required prior to the intrdocution of these outcomes into clinical practice and this remains an area for the future studies[76,77].

In conclusion, with the relatively high prevalence of childhood asthma, FOT has been proven to be a useful tool to aid in its diagnosis and management especially in children unable to perform spirometry. As the recent availability of commercial equipment has increased its use both in research and in clinical practice, clinicians have to understand the emerging role of FOT in clinical practice and how to interpret its results in order to optimise clinical management of children with asthma.

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ORIGINAL ARTICLE

Basic Study

Quantitative comparison of cranial approaches in the anatomy laboratory: A neuronavigation based research method

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Author contributions: Doglietto F performed the majority of experiments and wrote the paper; Qiu J developed the final, novel research method and contributed in most experiments; Ravichandiran M developed the first research methods and contributed to most experiments; Radovanovic I contributed to the research method development and participated in all experiments performed at the University of Toronto; Belotti F provided statistical analysis of the data and contributed to some experiments; Agur A provided anatomical supervision of the study and support for the first research methods; Zadeh G contributed to research method development; Fontanella MM provided supervision for the study in Brescia; Kucharczyk W and Gentili F provided full support and supervision of the study in all its phases.

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Abstract

AIM

To describe the development and validation of a novel neuronavigation-based method, which allows the quan-

tification of the anatomical features that define an approach, as well as real-time visualization of the surgical pyramid.

METHODS
The method was initially developed with commercially-available hardware for coordinate collection (a digitizer and a frameless navigation system) and software for volume rendering; dedicated neuronavigation software (ApproachViewer, part of GTx-UHN) was then developed. The accuracy of measurements and the possibility of volumetric rendering of surgical approaches simulated in a phantom were compared among three different methods and commercially-available radiological software. In the anatomy laboratory, ApproachViewer was applied to the comparative quantitative analysis of multiple neurosurgical approaches and was used by many surgeons who were untrained for the research method.

RESULTS
The accuracy of ApproachViewer is comparable to commercially-available radiological software. In the anatomy laboratory, the method appears versatile. The system can be easily used after brief training. ApproachViewer allows for real-time evaluation and comparison of surgical approaches, as well as post-dissection analyses of collected data. The accuracy of the method depends on the navigation registration: with a 1-2 mm registration error, it is adequate for evaluation and comparison of most neurosurgical approaches.

CONCLUSION
This new research method and software allows semi-automated visualization, quantification, and comparison of neurosurgical approaches in the anatomy laboratory.

Key words: Anatomical study; Comparison; Neurosurgical approach; Quantification; Research method; 3D rendering

Core tip: Herein, the authors describe the development and validation of a novel research method that allows quantification of the essential anatomical features of a neurosurgical approach and real-time rendering of its surgical volume. The measurements of ApproachViewer in a phantom with simulated approaches were noted to be largely homogeneous and comparable with those of other research methods. The authors further demonstrated the actual application of ApproachViewer in anatomical dissections to elaborate the advantages of real time 3D rendering and quantification. ApproachViewer provides a good alternative solution for fast 3D rendering and post-dissection analyses in a preclinical setting.

Doglietto F, Qiu J, Ravichandiran M, Radovanovic I, Belotti F, Agur A, Zadeh G, Fontanella MM, Kucharczyk W, Gentili F. Quantitative comparison of cranial approaches in the anatomy laboratory: A neuronavigation based research method. *World J Methodol* 2017; 7(4): 139-147 Available from: URL: http://www.wjgnet.com/2222-0682/full/v7/i4/139.htm DOI: http://dx.doi.org/10.5662/wjm.v7.i4.139

INTRODUCTION

Anatomical research is an essential phase of modern surgical innovation and evaluation[1], especially in an era of technological advancements, leading to the continuous improvement of different surgical approaches and techniques[2,3]. In the last two decades, different methods have been described for the quantification and comparison of neurosurgical approaches in the anatomy laboratory[4]. A common limitation of currently available research methods is the lack of visualization of the surgical pyramid that anatomically defines a neurosurgical approach (Figure 1)[4,5].

Herein, we present a novel neuronavigation based method that allows real-time visualization of the surgical pyramid, as well as quantification of its features and various post-dissection analyses. The development and validation process is described, together with some examples of the application of the method to evaluation and comparison of neurosurgical approaches in the anatomy laboratory.

MATERIALS AND METHODS

Four image-based systems were used to quantify and visualize the surgical pyramid[4,5] (Figure 1) in five simulated approaches (Figure 2). Every simulated approach was quantified 10 times with each research method. Data were then analyzed for intra- and inter-method variability (Figure 3). Two of the methods, based on neuronavigation systems, were also used to quantify surgical approaches in the anatomy laboratory.

Computed tomography scan

Computed tomography (CT) scans of phantom and anatomical specimens were performed using a 1 × 1 frame with contiguous slices, both at 1 and 3 mm (Somatom Definition Flash®, Siemens, Forcheim, Germany). CT was performed at a gantry of 0°, with a scan window diameter of 225 mm and a pixel size of more than 0.44 × 0.44. Images were recorded on a CD in DICOM format.

Quantification methods

The four research methods that were used to quantify and visualize the simulated surgical approaches are: (1) Radiological software (eFilm™); (2) digitizer and 3D rendering software (Autodesk Maya®); (3) navigation system and Autodesk Maya®; and (4) navigation hardware and a dedicated, new navigation software (ApproachViewer, part of GTx-UHN - Guided-Therapeutics software developed at University Health Network - Toronto, Canada).

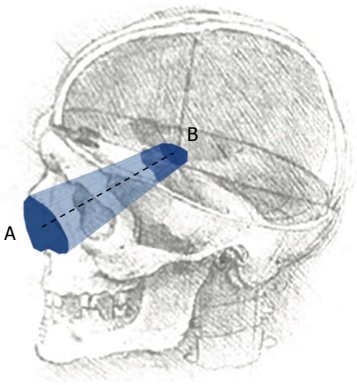

Figure 1 Schematic description of a surgical approach, as a "truncated pyramid"[4,5]: (1) Superficial surface (A), more commonly defined "surgical window" or "access area"; it represents the area through which instruments are introduced to work at the level of the deep area; (2) deep surface (B), usually defined "area of exposure", as it is the surface exposed by the approach; and (3) height of the truncated pyramid (dotted line). Volume and trajectory of this pyramid complete the essential anatomical definition of a neurosurgical approach. Background head image is from: Studies of human skull, Leonardo Da Vinci, supplied by Royal Collection Trust ©Her Majesty Queen Elizabeth II 2016.

Figure 2 A phantom was used to evaluate the accuracy of the methods used to quantify the surgical pyramid. Three funnels were positioned inside a radiotherapy mesh plastic mask to simulate a total of five different surgical approaches: Small funnel, simulating a narrow and short approach; medium funnel (asterisk), simulating two different approaches, with the same superficial area and different deep areas, at distinctive distances from the surface; large funnel, simulating two approaches, with the same superficial area and different deep areas, at the same distance. Round, one-millimeter metallic markers were positioned over the mask as reference points for neuronavigation registration (black arrow). A reference frame (white arrow) was attached to allow the use of navigation systems (see text for further details).

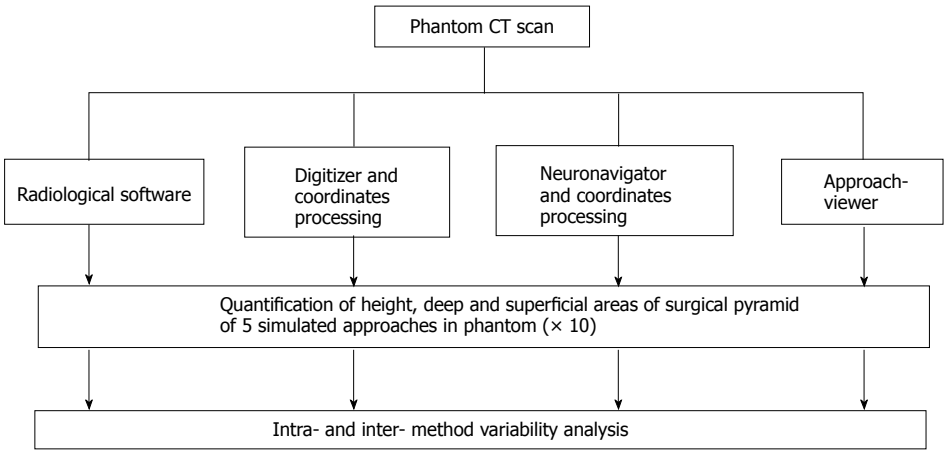

Figure 3 Study design. Each simulated approach was quantified 10 times with each of the research methods (see text for further details). CT: Computed tomography.

Radiological quantification: Commercially available radiological software that allows visualization in 2D and 3D of DICOM images was used (eFilm™, Merge Healthcare Incorporated)[6] to visualize and quantify the simulated approaches. The superficial and deep surfaces were calculated by dividing them in eight triangles; each triangular area was measured using Heron's formula (Figure 1 of online additional material). The height of the surgical pyramid was measured with the tool for linear distances (Figure 2 of online additional material)[6]. Three-D rendering of the approaches was performed, when feasible, using the volume rendering tools[6] (Figure 3A of online additional material).

Digitizer and Autodesk Maya®: MicroscribeTM 3DX Digitizer (Immersion Corporation, San Jose, CA, United States) consists of a base and digitizing arm with five degrees of freedom that terminates in a fine tip stylus (Figure 4 of online additional material). When the stylus tip is placed on a surface and a button is pressed, the Cartesian coordinates (x, y, z) of the point are recorded and stored in a computer as a text file. The digitizer mean accuracy is 0.23 mm[7]-0.5 mm[8].

Commercially-available software for image-based modelling and rendering (Autodesk Maya®) was used to build a 3D model of surgical approaches using collected coordinates (see Figure 3B of online additional material). MEL Script and Python programming languages were used to create a plug-in to import the coordinates into Autodesk Maya®. The resulting model could be manipulated in 3D and allowed visualization from any view. Using MEL, a script was created to measure: (1) Distance: The height of the truncated pyramid was calculated as the distance between the center points of the superficial and deep areas. The center points were determined by the centre of mass equation, using the 8 coordinates collected along the border of both superficial and deep surfaces; and (2) Area: The area

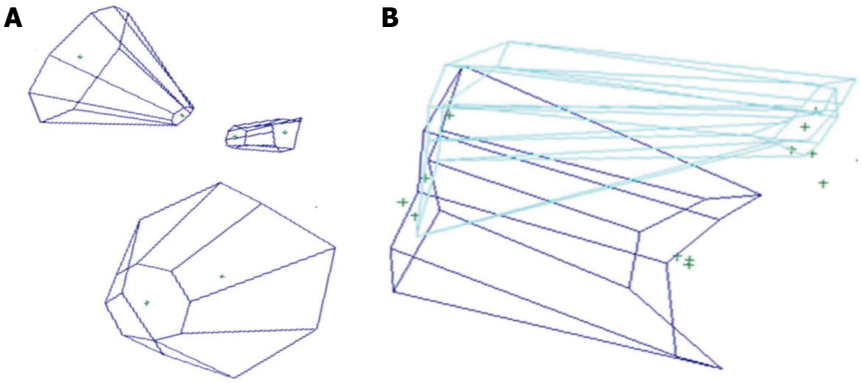

Figure 4 Volume rendering with Maya®. A: Visual rendering of three different funnels with the quantification method based on the commercially-available digitizer or navigation system and 3-D rendering software (Maya®); B: 3D rendering with the Storz navigation system for coordinate collection and Maya® software for 3D rendering of endonasal (light blue) and transoral (dark blue) approaches to the anterior craniovertebral junction.

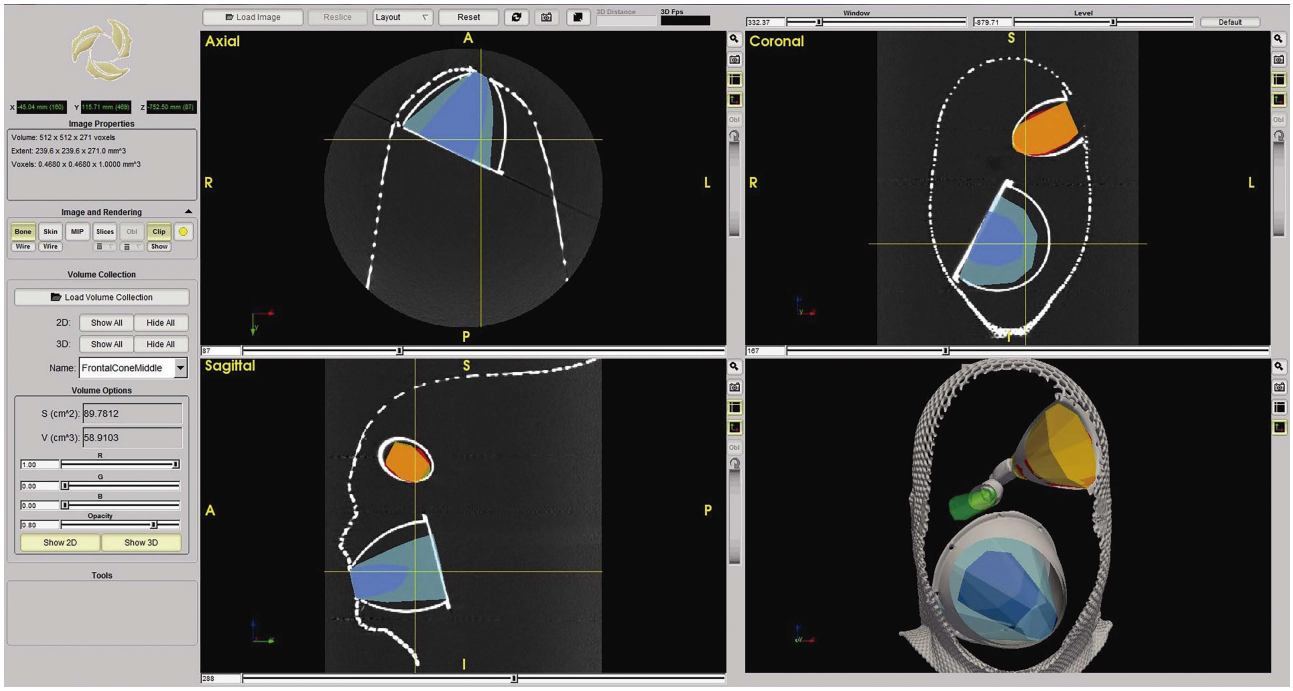

Figure 5 Rendering of the three funnels with ApproachViewer, which shows the five different approaches (in different colors) in the three axes and in 3D. The quantified volume of one of the simulated approaches is shown on the screen (see online additional material - ApproachViewer guide 1.0)

was calculated using the triangulation method. A vector was drawn to each of the 8 registered points from the center of mass equation. Two adjacent points along with the center formed a triangle, for a total of 8 triangles. Each triangular area was measured using Heron's formula.

Neuronavigation system and Autodesk Maya®: In the first phase of this study, we used a prototype created by Storz Company for ENT surgery (Karl Storz® ENT navigation system - Tuttlingen, Germany). The registration was based on four-point collection and neuronavigation was allowed when the mean registration error was less than 2 mm. This neuronavigation system provided the on-screen coordinates of a given point in millimeter values, including decimals (Figures 5 and 6 of online additional material). A screenshot of each point of interest was recorded using a commercially-available frame grabber (VGA2USB LR frame grabber, Epiphan, Ottawa, Canada) (see Figure 6 of online additional material). The coordinates were recorded on an Excel sheet, and then imported and elaborated in Autodesk Maya®, as described above.

ApproachViewer: Dedicated software, called ApproachViewer, part of GTx-UHN (Guided-Therapeutics software developed at University Health Network - Toronto, Canada), was developed to visualize the surgical pyramid inside the head in which the approach was being performed.

The used navigation hardware by NDI (Northern Digital Imaging®, Waterloo, Ontario, Canada) included:

Table 1 Results of the phantom quantification with 4 different research methods (see text for further details)

		e-Film™		Microscribe 3DX Digitizer®		Storz® navigator + Maya® reconstructions		ApproachViewer - GTx-UHN	
		mean	SD	mean	SD	mean	SD	Mean	SD
Height	Large MS	67	0.67	67.8	0.79	66.36	0.29	69.19	0.26
(mm)	Medium	48.3	0.48	52.5	0.23	47.51	0.31	48.7	0.55
	Small	38.3	0.67	40.46	1.11	36.98	0.56	38.9	1.03
Area	Large - deep	5310.19	43.50	4877.78	52.82	5461.03	35.56	6003.2	49.42
(mm^2)	Large - deep mid	1805.37	19.64	1548.06	15.45	1836.83	32.66	2073.4	40.85
	Large - superficial	441.87	21.22	416.81	12.11	409.05	12.62	533.3	16.44
	Medium - deep	NA	NA	128.24	5.45	136.89	4.73	201.4	7.41
	Medium - middle	NA	NA	498.69	14.01	NA	NA	470.4	21.80
	Medium - superficial	2425.57	46.34	2375.56	35.35	2555	20.86	2955.7	58.89
	Small - deep	82.49	6.37	108.34	4.92	90	4.24	125.4	6.88
	Small - superficial	150.84	12.70	161.43	5.54	168.3	11.36	256.1	11.40

Area values are expressed in mm^2; height values are in mm. SD: Standard deviation; Mid: Area included in the deep surface (mid-area); NA: Not available.

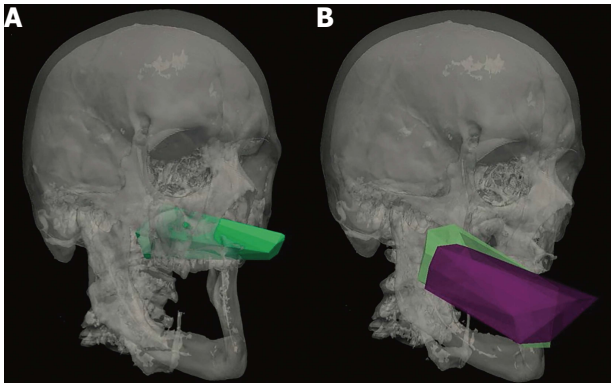

Figure 6 Visual rendering of anterior approaches to the odontoid with ApproachViewer. A: Endonasal endoscopic approach to the anterior craniovertebral junction (CVJ); B: Transoral without (purple) and after soft palate split (green) approaches to the CVJ.

(1) A passive rigid body (Rigid body 2®); (2) a passive probe with 4 markers; and (3) Polaris Vicra Optical Tracking System.

Circumferential points of the superficial and deep surfaces of each funnel were collected using the pointer tool. The surface points were then projected to the best plane fit using linear least squares. Delaunay triangulation was used to generate triangles on the plane and Heron's formula applied. The height of each funnel was measured as the distance between the center of the superficial and deep surfaces.

Data collection and statistical analysis

Each simulated approach was quantified 10 times with each research method. Mean values and standard deviation of each value were calculated. Data were collected in Excel (Microsoft®, United States) and analyzed with OriginPro® (OriginLab®, Northampton, MA, United States). Standard deviations of the different methods were compared calculating the coefficients of variation (CVs) for each, in order to test their precision[9]. In addition, Brown-Forsythe tests for homogeneity of variances (HOV) were performed by comparing ApproachViewer to the other quantification methods. The level of significance for Brown-Forsythe test was set at 0.05.

The statistical methods of this study were reviewed by Elena Raffetti from Epidemiology and Public Health Intervention Research group (EPHIR), Department of Public Health Sciences, Karolinska Institutet.

Anatomical dissections

Anatomical dissections and data collection were performed at the University of Toronto Surgical Skills Centre at Mount Sinai Hospital. REB approval was obtained (UHN REB number: 09-0130-T) (Figure 6 of online additional material).

Dissections were performed under 3 to 40 microscopic magnifications (Carl Zeiss® Surgical Microscope) and with 0º and 30º, 4 mm endoscopes (Karl Storz® - Tuttlingen, Germany). Various microsurgical and endoscopic approaches to the skull base and to certain intracranial areas were performed. In the first phase of this study, they were quantified with a commercially-available neuronavigation system connected to a frame grabber and coordinate elaboration with Autodesk Maya®, as described above. In the second phase of the study, ApproachViewer was always used.

RESULTS

Comparative analysis

Table 1 summarizes the results of the quantification of height, deep, and superficial areas of the phantom funnels with all 4 methods. CVs were less than one in all cases, indicating that all methods have low variance distributions.

The Brown-Forsythe tests showed that variances of ApproachViewer quantifications were homogeneous with those of the other methods, with two exceptions. Homogeneity of variances (HOV) was not verified comparing ApproachViewer to the digitizer for either medium or large funnels heights. On the contrary, HOV was statistically valid comparing ApproachViewer to e-Film and Storz navigation quantifications ($P < 0.05$).

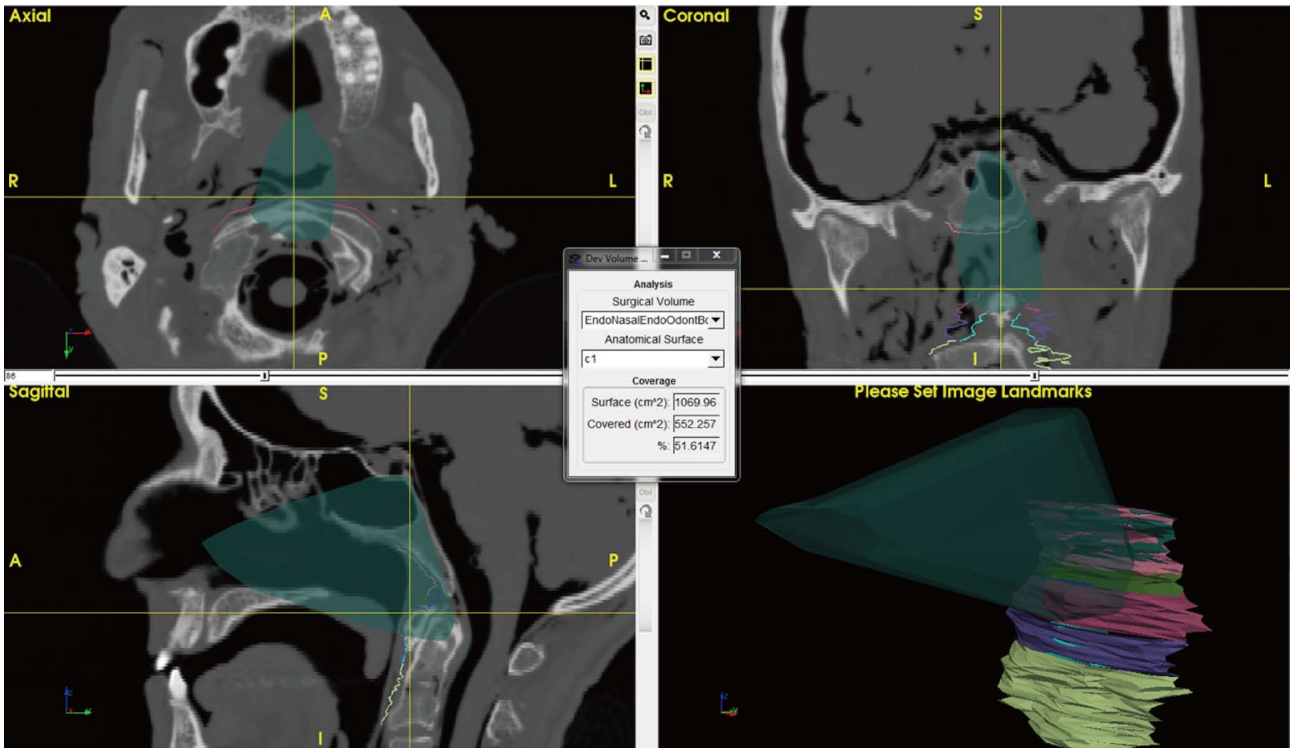

Figure 7 Detail of ApproachViewer screen during post-dissection analyses. An endonasal endoscopic approach to the odontoid was performed in the anatomy laboratory and is retrieved and visualized in the three axes and as a volume. Different areas of interest have been contoured at the level of the anterior craniovertebral junction. The box at the center shows the absolute and percentage value of contoured C1 exposed by the approach (see online additional material - ApproachViewer guide 1.0 for further details).

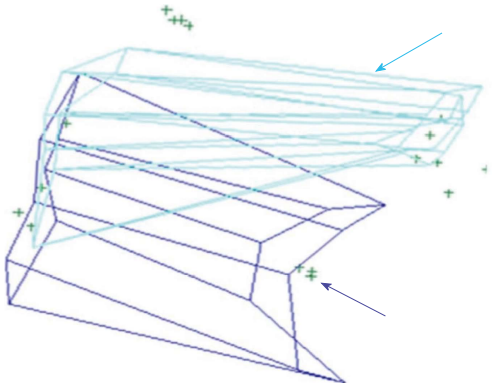

Figure 8 Three-D rendering of endonasal endoscopic (light blue) and transoral with soft palate split (purple) approaches to the anterior craniovertebral junction

3D visualization

Figures 4A and 5 show volume rendering of the simulated approaches, obtained with newly developed system (*i.e.*, navigation system and Maya® software; ApproachViewer - GTx-UHN). The results are visually comparable to the those obtained with commercially-available radiological software (eFilm™) (Figure 3 of online additional material).

Anatomical dissections

Figures 4B and 6 show 3D rendering of surgical approaches that were quantified with both navigation-based research methods (*i.e.*, navigation system and Maya® software; ApproachViewer - GTx-UHN) in the anatomy laboratory (see also Figures 7 and 8 of online additional material for examples of rendering with the navigation system and Maya® software).

The mean time to obtain the 3D rendering of an approach with the navigation system and Maya® software was approximately 2-4 min for coordinate collection (8 points for each of the surfaces were collected; 2 people were needed), 3-8 min for coordinates registration in an Excel file (whether performed by one or two people), and 5 min for rendering with Maya®. The mean time to obtain the 3D rendering of an approach with ApproachViewer was 2 min, *i.e.*, the time needed to collect multiple points both at the deep and superficial surface. Rendering was therefore immediate with ApproachViewer, while it was possible only after the laboratory session with the previously developed system.

Additional features were developed with ApproachViewer, which was the only system that allowed visualization of approaches taking place inside the head in which they were performed. Areas of interest were contoured: ApproachViewer automatically calculated the absolute and percentage value of the area included in a specific approach (Figure 7). This feature was used in the post-dissection phase of anatomical studies (ApproachViewer guide 1.0 for further details, available from the corresponding author).

DISCUSSION

Comparative analysis

The comparative analyses documented a satisfactory, limited variation in the calculated data for each of the research methods, according to their CVs. Variation was more significant when different research methods were compared. We believe that this variability is due to different reasons, as recently reported by Ammirati's group[9], possibly including different registration errors, varying methods to calculate the areas, and differing methods to collect the coordinates.

A digitizer is possibly the instrument for coordinate collection with the lowest error (0.23 mm[7] - 0.5 mm[8]). Its role in the analysis of surgical approaches is, however, limited by the physical constraints caused by its dimensions and desktop-based nature. The only statistically significant differences between the different methods were most probably due to the difference in coordinate collection, due to the physical constraints caused by the digitizer arm. Frameless navigation systems might have relatively higher errors, but have the advantage of high flexibility for coordinate collection, and have therefore been used extensively in recent anatomical studies[4]. The registration error of neuronavigation can be decreased using well recognizable registration points, such as screws that can be positioned around the area of interest[9].

3D visualization and quantification

The research method based on the use of a commercially-available navigation system and Maya® 3D rendering software provided 3D visualization and quantification of the truncated surgical pyramid that defines a surgical approach. A visual comparison of different approaches was therefore possible (Figure 4B), but to provide the correct orientation in space of each surgical pyramid a common registration had to be provided (*i.e.*, three fixed points were registered during each session). This system, which was developed in 2009, provided for the first time the visualization in 3D of the surgical approach. The method is similar to others that have been recently published[4]. An evident practical limit of the method was the lengthy data elaboration process, which included manually copying the coordinates from each screenshot in an Excel sheet and manually superimposing the registration points in the 3D rendering of the pyramid. These issues may have been partially resolved, but the main limit that stopped us from further developing this research method was the impossibility of automatically visualizing the head in which the coordinates had been collected. It would have been possible to manually superimpose surgical volumes and CT images, but this would have introduced another possible cause of error and bias.

ApproachViewer in the anatomy laboratory

ApproachViewer was therefore developed as it allows visualization of the surgical volume inside the specimen in which the approach has been performed.

A new feature was then developed to further advance the objective evaluation of neurosurgical approaches. Once dissection sessions are over, areas of interest can be contoured. The software then allows the automatic quantification of absolute and percentage values of the area of interest that is included in each surgical approach (Figure 7 and ApproachViewer guide 1.0). We believe that this brings to reality a research method that was foreseen by Andaluz *et al*[5] more than 10 years ago: "We envision the ideal comparison between approaches as a volumetric analysis of truncated pyramids with polyhedral bases, with a special interest in the top of the pyramid. The incremental presence of computer-assisted devices in cranial base laboratories may some day bring this near-science-fiction concept into real numbers".

When compared to other research methods based on navigation systems, ApproachViewer provides quantifications with the same precision, direct visualization of the surgical pyramids, and the possibility of using tools to measure areas of sections of the pyramids and to measure the distances between them to obtain heights (such as the middle surface of the medium funnel in the present study, which could not always be obtained with other methods). Compared to how we started, when we had to manually transcribe each coordinate into a separate database, which would then be elaborated, ApproachViewer is incredibly more user-friendly and faster, with automatic recording and calculations of pointer movements and positions, and thus automatic determination of pyramid dimensions and volumes. Use of the system should be intuitive to neurosurgeons who use any neuronavigation system in their surgical practice, as the same instruments, reflective spheres, and stereoscopic camera are used. Moreover, the system was used extensively by surgeons and medical students at the University of Brescia: Its use appears to be intuitive and easy to use (see ApproachViewer guide 1.0), although further studies are necessary to confirm these preliminary data.

The group led by Ammirati has recently described a method that allows visualization and quantification of the volume of a surgical approach[4,10]. The method is based on filling the surgical cavity with fat and CT scanning after dissection; the volume is then quantified with neuronavigation software. The main limit of the method is the need for post-dissection CT after each approach is performed[4], while ApproachViewer allows the collection of multiple data in a dissecting session without the need for multiple CT scans. On the other hand, it quantifies the surgical pyramid defined by a deep area and superficial one, which need to be defined before the dissections are performed.

The potential applications of ApproachViewer are multiple: (1) It provides a user-friendly method to quantify and therefore compare different surgical approaches; (2) as the working volume of the approach is immediately visualized on a screen, it can provide

immediate feedback to a surgeon in training; and (3) the quantification of the working space has important implications for the development of angled instruments, especially for endoscopic skull base surgery.

In the past few years ApproachViewer has been systematically applied to the analysis of multiple skull base approaches: Some results have already been published[11-14]. All these potential applications require specific studies, possibly by multiple centers.

We have developed and validated a new, navigation-based tool for anatomical research in neurosurgery. ApproachViewer (part of part of GTx-UHN - Guided-Therapeutics software developed at University Health Network - Toronto, Canada) provides the possibility of multiple data collection during dissection sessions, as well as various post-dissections analyses, including 3D rendering of the surgical volume, quantification of the anatomical features that define a surgical approach, and of the area of interest exposed.

COMMENTS

Background

Anatomical studies are an essential part of the preclinical phase of surgical research. They can provide objective, quantitative, comparative data that can be used to evaluate novel surgical approaches and techniques.

Research frontiers

Different research methods have been described to quantify and compare different surgical approaches and most of them do not provide visual rendering and quantification of the surgical pyramid, which is the working volume that defines a neurosurgical approach.

Innovations and breakthroughs

This study describes the development and validation of a novel neuronavigation-based method, which allows the quantification of the anatomical features that define an approach, as well as real-time visualization of its surgical pyramid.

Applications

ApproachViewer has already been extensively used in the anatomy laboratory to quantify and compare different neurosurgical approaches. It provides a real-time visualization and quantification of the surgical pyramid. Possible applications include not only the preclinical quantification of surgical approaches, but also: (1) Immediate feedback to surgeons in training in the anatomy laboratory during dissections; (2) Detailed analysis of the surgical volume for the development of new surgical instruments; and (3) Quantification of the working volume in clinical scenarios.

Terminology

Neuronavigation: Computer-assisted technologies used to guide or "navigate" within the intracranial space.

Peer-review

The exposition is well conducted and the topic is very interesting.

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CASE REPORT

Laparoscopic-extracorporeal surgery performed with a fixation device for adnexal masses complicating pregnancy: Report of two cases

Hanako Kasahara, Iwaho Kikuchi, Aya Otsuka, Yoko Tsuzuki, Michio Nojima, Koyo Yoshida

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Author contributions: Kasahara H and Kikuchi I contributed equally to this work; Kasahara H, Kikuchi I, Otsuka A and Tsuzuki Y performed the research; Kikuchi I designed the research; Nojima M and Yoshida K conducted the research; Kasahara H wrote the paper.

Informed consent statement: Because the patients have moved, we could not contact them. Before the operation, we have got comprehensive agreement, so the IRB approved.

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Abstract

The potential complications associated with an adnexal mass discovered during early pregnancy call for surgical treatment. Ideally, surgery is performed after gestational week 12, but uterine expansion after the first trimester makes surgery difficult. We report two pregnancies complicated by adnexal masses for which we used an organ fixation device for safe performance of single-site umbilical laparoscopic surgery. Pelvic magnetic resonance imaging depicted a dichorionic, diamniotic twin pregnancy and 60-mm right adnexal mass in the first patient and bilateral adnexae in the second. All three masses were suspected mature cystic teratomas. Both patients underwent laparoscopic surgery during gestational week 14. With use of an organ fixation device, traction was applied until the mass reached the umbilicus; tumor resection was performed extracorporeally. In the second patient, the second mass was simply aspirated because adhesions were encountered. Our single-site laparoscopic-extracorporeal technique proved to be a safe approach to an otherwise high-risk situation.

Key words: Laparoscopic surgery; Pregnant complication; Ovarian mass; Fixation device; Extracorporeal

Core tip: The new device, "Ova-Lead" has a 20-mm-diameter tip that is made of silicone and shaped like a suction cup. It fixes to the organ through the application of negative pressure, by using this device the surgeon manipulates the organ. We reported two cases of adnexal mass discovered during pregnant that this device seemed useful.

Kasahara H, Kikuchi I, Otsuka A, Tsuzuki Y, Nojima M, Yoshida K. Laparoscopic-extracorporeal surgery performed with a fixation

device for adnexal masses complicating pregnancy: Report of two cases. *World J Methodol* 2017; 7(4): 148-150 Available from: URL: http://www.wjgnet.com/2222-0682/full/v7/i4/148.htm DOI: http://dx.doi.org/10.5662/wjm.v7.i4.148

INTRODUCTION

One or more adnexal masses are discovered in a reported 0.01%-1% of all pregnancies[1]. The majority resolve spontaneously, but in some cases, torsion or rupture necessitates emergency surgery. Ideally, surgery is performed after gestational week 12, but expansion of the uterus after the first trimester makes surgical manipulation difficult. We report adnexal masses complicating 2 pregnancies for which we used an organ fixation device for safe performance of single-site umbilical laparoscopic surgery.

CASE REPORT

Case 1

The patient was a 29-year-old woman, gravida 0 para 0. An early-stage dichorionic, diamniotic twin pregnancy was confirmed simultaneously with a right-sided adnexal mass. Pelvic magnetic resonance imaging (MRI) revealed a 60-mm mass that appeared to be a mature cystic teratoma, so laparoscopic surgery was scheduled and performed during gestational week 14. We placed Lap Protector and EZ Access (Hakko Corporation Tokyo Japan) as a wound retractor in the umbilicus, and we used an organ fixation device called "Ova-Lead" (Fuji Systems corporation, Tokyo Japan) to apply traction to the adnexa to bring the mass up to the umbilicus (Figure 1). We resected the mass extracorporeally (Figure 2). She was followed up at our hospital until 22 wk then moved overseas.

Case 2

The patient was a 38-year-old woman, gravida 0 para 0. Bilateral adnexal masses were identified during the early stage of pregnancy. Pelvic MRI revealed a 70-mm left adnexal mass and a 50-mm right adnexal mass. Both were thought to be mature cystic teratomas, so laparoscopic surgery was scheduled and performed during gestational week 14. We placed a RapidPort EZ Access Port in the umbilicus. We encountered extensive adhesions within the peritoneal cavity. Traction was applied to the left adnexa by means of an organ fixation device, "Ova-Lead" until the mass reached the umbilicus, and the mass was resected extracorporeally. Applying traction to the right adnexa proved difficult due to the adhesions, so we simply performed paracentesis. The fluid contained hemorrhagic components, so we suspected an endometrioma. The left adnexal mass was diagnosed histologically as a mixed cystic teratoma and endometrioma. No recurrence of the right mass was noted during the remaining course of the pregnancy.

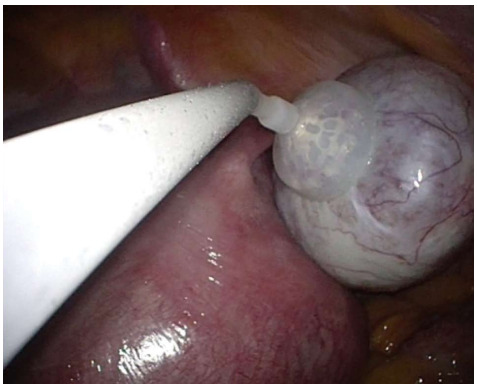

Figure 1 By using "Ova-Lead", aspirate sucking and fix the ovaries to the cup.

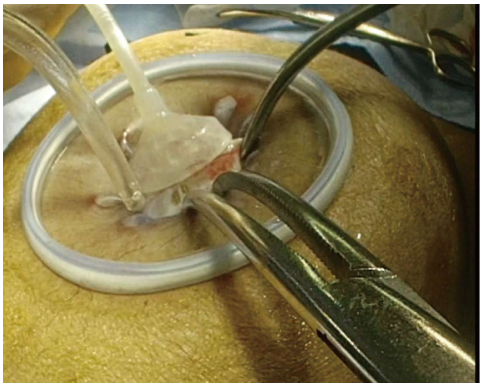

Figure 2 Ovarian cystectomy was performed extracorporeally after pulling out the whole ovary from the abdominal cavity.

She was followed up at our hospital, and at 36 wk, premature rupture of membrane occurred to her, then she was delivered vaginally.

DISCUSSION

The "Ova-Lead" has a 20-mm-diameter tip that is made of silicone and shaped like a suction cup. It fixes to the organ through the application of negative pressure (30 mmHg). The surgeon manipulates the device by a metal handle, and use of the device eases performance of the operation. At our hospital, we attach and fix the device to the adnexal mass and then apply traction to the mass to draw it up to the umbilicus. This allows us to resect the organ extracorporeally, and by using this single-port technique, the operation time is shortened, and surgery can be performed with as little leakage of tumor contents into the peritoneal cavity as possible.

Adnexal masses occurring during pregnancy are of various tissue types. The most common are mature cystic teratomas, representing 40% of adnexal masses. These are followed in order by serous cystadenomas at 20%, mucinous cystadenomas at 10%, endometriomas at 5%, and malignant tumors at 3%[1]. The contents of a mature cystic teratoma can easily leak into the peritoneal cavity. This has been found to result in

chemical peritonitis. Therefore, at our hospital, we use an extracorporeal technique to resect the mass.

Extracorporeal resection generally reduces the overall operation time, thus shortening the pneumoperitoneum time. Jansen *et al*[2] verified that increases in intrauterine pressure can result in fetal hypoxia. Hunter *et al*[3] verified in an animal model that carbon dioxide (gas) pneumoperitoneum can cause fetal acidosis and noted that changes were greatest at pressures of 15 mmHg or more. We believe that laparoscopic-extracorporeal resection, in comparison to total intracorporeal laparoscopic resection, allows us to better shorten the duration of both the surgery and the pneumoperitoneum, helping us prevent this complication.

Adverse events can occur in pregnant women with an adnexal mass. There is potential for pedicle torsion (1%-22%), rupture (9%), miscarriage or premature labor (5%-15%), or infection (1.2%-2.4%)[4]. The risk of such complications increases when the mass is greater than 6 cm[4]. We recommend surgery for masses greater than 6 cm that we encounter at our hospital.

Our gynecology department guidelines recommend performing surgery after gestational week 12, after the period of organogenesis has passed. The Japan College of Radiology imaging guidelines recommend use of MRI after gestational week 14. Surgery becomes increasingly difficult with each passing gestational week, so at our hospital, we perform surgical treatment as close to gestational week 14 as possible if a diagnosis has been made by then.

In conclusion, we treated two cases of adnexal masses complicating pregnancy by performing single-port umbilical laparoscopic surgery, using an organ fixation device, and resecting the masses extracorporeally. There are risks associated with surgery performed during pregnancy, but the potential complications associated with the simultaneous presence of an adnexal mass outweigh the risks of surgery. We have found that our technique prevents the complications associated with such surgery and facilitates safe surgical treatment even when the surgical field is difficult to secure and the uterus is especially enlarged, as in the case of a twin pregnancy. And also, even in the case of a large ovarian tumor, this method was suggested to be useful.

ARTICLE HIGHLIGHTS

Clinical diagnosis

Ovarian cyst (benign).

Differential diagnosis

Ovarian carcinoma, *etc.*

Imaging diagnosis

Magnetic resonance imaging findings as follows: Case 1: Mature cystic teratoma; Case 2: Endometrioma.

Pathological diagnosis

Case 1: Mature cystic teratoma; Case 2: Endometrioma.

Treatment

Surgical treatment.

Related reports

This manuscript was the first report about this device.

Experiences and lessons

In the case of a large ovarian tumor, this “ova-lead” was suggested to be useful.

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