Title: METHODS FOR DETERMINING PERCENT AGE-PREDICTED EXERCISE CAPACITY IN WOMEN

Abstract: Methods, systems and apparatus for determining percent age-predicted exercise capacity for women using a nomogram for percent age-predicted exercise capacity developed from a large study of asymptomatic women are provided.
METHODS FOR DETERMINING PERCENT AGE-PREDICTED EXERCISE CAPACITY IN WOMEN

FIELD OF INVENTION

[0001] This invention relates to methods, systems and apparatus for determining percent age-predicted exercise capacity for women using a nomogram for percent age-predicted exercise capacity developed from a large study of asymptomatic women.

BACKGROUND

[0002] Exercise capacity has been shown to be an independent predictor of mortality and future cardiac events in asymptomatic women and men.\(^1\)\(^-\)\(^5\) Exercise capacity is an estimate of the maximal oxygen uptake for a given workload,\(^6\)\(^,\)\(^7\) and can be measured by performing a symptom-limited stress test. Exercise capacity may be expressed in units of metabolic equivalents (MET), where a MET is a measure of ventilatory oxygen consumption expressed as multiples of basal resting requirements. One MET is one unit of basal oxygen consumption, which equals 3.5 ml-body oxygen consumption per kilogram body weight per minute for an average adult.\(^8\)

[0003] There are numerous exercise stress testing protocols developed for different patient populations. The more rapidly paced protocol (Bruce, Ellestad) are best for assessing younger and more active populations. The more moderate protocols are best suited for older or deconditioned patients (Naughton, Balke-Ware).\(^9\) The usefulness of having a common workload measurement allows the measurement of exercise capacity to be translatable to all exercise stress protocols, where the workload achieved can be translated into METs.

[0004] Exercise capacity is dependent upon age, as well as gender and disease state. A number of studies have established that there is a negative linear relationship between exercise capacity and age in men and a nomogram has been established for men, estimating percent-predicted exercise capacity achieved relative to age.\(^6\)\(^,\)\(^7\)\(^,\)\(^10\)\(^-\)\(^12\) A number of regression equations for predicting exercise capacity in a variety of male
populations have been described.\textsuperscript{6, 7, 10-12} Only two studies directly measured maximal oxygen uptake,\textsuperscript{6, 10} whereas the remainder estimated the exercise capacity, based on the speed and degree of incline achieved. Three of these studies examined the relationship of exercise capacity to age in healthy male volunteers.\textsuperscript{6, 7, 10} In contrast, there have been few studies evaluating exercise capacity in women, and to date, determinations of normative values of exercise capacity for age in women have not been well established and no nomogram has been established for women.

**SUMMARY**

[0005] A nomogram for predicting percent age-predicted exercise capacity in women has been developed. The nomogram was based on a study of a group of women and, for women, provides more accurate results than other presently available nomograms that were based solely on studies of men. The percent age-predicted exercise capacity may be related to cardiac death rates and all-cause mortality in women. Methods, systems and apparatus which implement the nomogram are also provided.

[0006] The nomogram has two outer scales, one for a woman's actual (i.e., measured) exercise capacity and a one for the woman's age. A center scale represents percent age-predicted exercise capacity. The intersection between a line connecting a woman’s actual exercise capacity and the woman’s age and the center scale provides the woman’s percent age-predicted exercise capacity. The nomogram may be applied to both symptomatic woman (e.g., women that have been referred for testing by a physician or other health care professional) or asymptomatic (e.g., healthy or seemingly healthy) women.

[0007] The invention also provides a computer program for determining percent age-predicted exercise capacity in women. The program includes computer code adapted to determine where a line connecting a woman’s actual exercise capacity and the woman’s age would intersect the line representing percent age-predicted exercise capacity in a nomogram based on a study of a group of women. The computer program may be incorporated into a computer system that includes a central processing unit, an input interface for transmitting a woman’s actual exercise
capacity and age to the central processing unit and a memory storage medium for storing the computer code.

[0008] Also provided is a testing apparatus for determining a woman’s percent age-predicted exercise capacity. This apparatus may include the computer system described above and an exercise platform, such as a treadmill or a stepping stool. While the woman is exercising on the exercise platform her exercise capacity is measured and input into the input interface of the computer system. The woman’s age is also input into the system. Based on these inputs, the computer code is used to calculate the woman’s percent age-predicted exercise capacity. A variety of protocols may be used to determine the woman’s exercise capacity. These include, but are not limited to, the Bruce protocol, the Ellestad protocol, the Naughton protocol and the Balke-Ware protocol.

[0009] Further objects, features and advantages of the invention will be apparent from the following detailed description when taken in conjunction with the accompanying drawings.

**BRIEF DESCRIPTION OF THE DRAWINGS**

[0010] FIG. 1. Regression equation of exercise capacity (in METs) versus age (in years) for asymptomatic women. Inner lines represent 95% confidence limits for the mean; outer lines represent 95% prediction limits.

[0011] FIG. 2. Nomogram of percent age-predicted exercise capacity (in METs) for age in asymptomatic female volunteers.

[0012] FIG. 3. Nomogram of percent age-predicted exercise capacity (in METs) for age in sedentary and active asymptomatic female volunteers.

[0013] FIG. 4. Illustrative nomogram for percent age-predicted exercise capacity for two women, ages 60 and 30, with a measured MET level of 7.

DETAILED DESCRIPTION

[0015] In order to adequately assess an individual’s exercise capacity requires a comparison with standard exercise capacities. However, standard exercise capacity for a particular group will vary depending upon such factors as age, activity status, health and gender. It follows that the relevant standard exercise capacity for women should be based on a study of women. Unfortunately, prior to the present invention no such women-specific standards were available.

[0016] The present methods and systems for calculating a predicted exercise capacity for women and for determining the percent of predicted exercise capacity for a woman were developed through the study of a large sample of women of different ages. The percent predicted exercise capacity for women provides a predictor of cardiac death rates and all-cause mortality in women based on the results of a relatively simple stress test.

[0017] The full details of the studies from which the present methods were developed are presented below. Briefly, a group of nearly 6000 asymptomatic (i.e., lacking symptoms of heart disease) women underwent a symptom-limited stress test using the Bruce protocol and exercise capacity was measured in metabolic equivalents (METs). A univariate linear regression was performed with age as the independent variable and MET as the dependent variable. The resulting linear regression equation for predicted exercise capacity based on age was:

\[
\text{exercise capacity} = 14.7 - 0.13 \times \text{(age of woman)}, \quad (1)
\]

\[
(n = 5721; \text{SD} = 2.3; r = -0.51; P < 0.001)
\]

where \( n \) is the number of women in the study and SD is the age-adjusted standard deviation. Thus, equation (1) can be used to calculate a nomogram for percent age-predicted exercise capacity from the exercise capacity values that are equal to 14.7-0.13 \( \times \) (age or woman), within a SD of the estimate of 2.3 or better and a \( P \) value < 0.001.

[0018] The percent age-predicted exercise capacity achieved for a given age was then obtained using the following equation:
% age-predicted exercise capacity = (Actual MET Level/exercise capacity) x 100, (2)

where exercise is measured in MET levels in accordance with equation (1). Thus, the percent age-predicted exercise capacity represents the percent age-predicted exercise capacity for a given age based on measured MET Level, where 100% represents the average for a given age.

[0019] Values for the percent age-predicted exercise capacity (from 20% to 150%) were calculated using equation 2. A nomogram for the healthy population was plotted using specific ages and observed MET levels for different values of exercise capacity. A best fit line was then drawn through the intercepts for the percent age-predicted exercise capacity for age to complete the nomogram.

[0020] The nomogram is very simple to use, requiring only the woman’s age and actual exercise capacity (in METs) as measured by an exercise stress test for any stress protocol. Drawing a line between the age and actual exercise capacity will allow the determination of the percent predicted exercise capacity for age, where 100% predicted exercise capacity is the mean normal for any given age. Anything greater than 100% indicates better than average performance. Anything lower than 100% indicates some degree of functional capacity impairment for age.

[0021] In addition to providing methods for determining percent age-predicted exercise capacity for women, the present invention provides systems and apparatus for implementing the methods. One such system includes a central processing unit, an input interface for transmitting inputs to the central processing unit and a memory for storing the predicted exercise capacity nomogram. In addition a computer program product including a set of instructions for calculating a percent age-predicted exercise capacity from a patient’s age and actual MET level, using the methods described above, may be embedded in computer code stored in the memory. Thus, in practice the interface is used to input a woman’s age and actual MET level and the stored nomogram is used to convert these inputs into a calculated percent age-predicted exercise capacity. The system may also optionally include a display unit and/or a printer for displaying and/or printing the calculated percent age-predicted exercise capacity.
Examples of suitable storage media include, but are not limited to, random access memory, read-only memory, a CD and a disc. Examples of suitable input interfaces include, but are not limited to, keyboards, touch screens, voice-activated systems and digital interfaces. Examples of suitable display units include, but are not limited to, a computer monitor, a digital screen and a liquid crystal display.

The system may be integrated into a stress testing or exercise apparatus adapted to collect exercise capacity data in the form of METs from a patient. The components of the apparatus may vary depending upon the nature of the stress testing protocol to be performed. However, the apparatus will generally include an exercise platform, such as a treadmill or a steaping stool. In some embodiments the system may further include a patient interface for measuring physiological data from the patient. For example, the system may include a mask for measuring expired oxygen and exhaled carbon dioxide. In practice data collected from a woman on the exercise platform is converted into exercise capacity data in the form of METs which are provided to the system central processing unit through the input interface.

A more detailed description of the study used to develop the present methods is provided below. This description is provided solely to assist one of skill in the art in understanding and using the present invention and should not be interpreted as limiting the scope of the invention.

The purpose of the study was to create a simple nomogram for women to allow the translation of the MET level achieved on a stress test into a percent of normal exercise capacity for women for any age, based on a population of asymptomatic women. The results of the study were validated by a symptomatic, referral-base population of women to determine the usefulness of this nomogram in clinical practice.

**METHODS:**

**Asymptomatic Population**

The asymptomatic population came from the St. James Women Take Heart Project. The St James Women Take Heart cohort has been described in full
Previously, briefly, in 1992 a call for volunteers from the greater Chicago metropolitan area resulted in a cohort of 5932 asymptomatic women. Inclusion criteria were age 35 years or older, the absence of active cardiovascular disease and ability to walk on a treadmill at a moderate pace. Women were excluded if they were pregnant or had experienced typical anginal symptoms or myocardial infarction within the previous 3 months, weighed over 325 pounds or had blood pressures of 170/110 mm-Hg or higher before initiating the stress test.

[0027] All participants underwent a physical examination. During the recording of the baseline resting ECG, supine blood pressures were measured by technicians test using standard clinical procedures. Standing blood pressures were recorded prior to the start of the exercise treadmill. Activity status of this population was classified into sedentary and active groups, based on the response to one question: Do you have a regular (exercise) training program?

[0028] Study-specific exclusion criteria included the following: 1) Performance of the modified-Bruce Protocol (n=109); 2) Presence of any cardiac disease, including previous myocardial infarction, documented CVD, heart failure, or valvular heart disease (n=91); 3) Those with incomplete data concerning cardiac risk factors (n=11).

[0029] All-cause mortality was determined using a National Death Index Search was to identify all deaths from after the baseline evaluation in 1992, up to the end of year 2000.

Referral Population

[0030] The referral population has been previously described. Briefly, these women were prospectively enrolled and followed from 1990 to 1995. This cohort was composed of 4471 consecutive women from 6 medical centers who were referred for a symptom-limited exercise stress test using the Bruce protocol for evaluation of suspected coronary disease. Women were excluded if they had been recently hospitalized for unstable angina, myocardial infarction and coronary revascularization.
Follow-up information was obtained on this referral population by clinic visit or telephone interview. Deaths were identified and cause of death was classified after review of death certificates by an independent reviewer, unaware of the patient’s clinical history or stress testing data.

**Exercise Treadmill Testing**

Participants underwent a symptom-limited treadmill test according to the Bruce protocol with exercise ECG measurements. Heart rate and blood pressure were measured and a 12-lead ECG was recorded before exercise, at the end of each exercise stage, at peak exercise and at 1-minute intervals during recovery. The test was discontinued for limiting symptoms (angina, dyspnea, fatigue), abnormalities of rhythm or blood pressure, or marked and progressive ST segment deviation. Target heart rates were not used as a predetermined end point.

**Exercise Capacity**

Exercise capacity was measured in units of metabolic equivalents (MET) and is an estimate of the maximal oxygen uptake for a given workload. A MET is a measure of ventilatory oxygen consumption expressed as multiples of basal resting requirements; where one MET is one unit of basal oxygen consumption, which equals 3.5 ml-body oxygen consumption per kilogram body weight per minute for an average adult. The exercise capacity (in MET) was estimated by the speed and the grade of the treadmill.

**Statistical Analysis**

Using the asymptomatic population, simple univariate linear regression was performed with age as the independent variable and exercise capacity (in METs) as the dependent variable. The relationship was established in the asymptomatic, healthy cohort.

The observed MET achieved was obtained from the final treadmill speed and grade, as defined for the Bruce stress test. The percent age-predicted
exercise capacity achieved for a given age was then obtained using the following equation:

\[ [0036] \quad \text{Percent age-predicted exercise capacity achieved} = \left( \frac{\text{Actual MET Level}}{\text{Age-Predicted MET Level}} \right) \times 100\% \]

[0037] The percent age-predicted exercise capacity represents the percent age-predicted exercise capacity for a given age based on the MET performed, where 100% represents the average for the given age. Values for percent age-predicted exercise capacity (from 20% to 150%) were calculated using the equation above. A nomogram for the healthy population was plotted using specific ages and observed MET levels for different values of exercise capacity, where a best-fit line was drawn though the intercepts for the percent age-predicted exercise capacity for age. Similarly, a nomogram was created for both the active and sedentary groups.

[0038] Validation of the regression line predicting exercise capacity for any given age was performed using both the asymptomatic women and the referral population. Cardiac death rates were plotted against the ratio of observed-to-expected exercise capacity. All-cause mortality and cardiac mortality was analyzed for both populations using Kaplan-Meier survival curve analysis and univariate Cox proportional hazards models, based on deviation from the predicted normal value of exercise capacity for age in both populations. Annualized death rates were calculated for the referral population, by taking the estimated death rates from the Cox model, and dividing it by the time of follow-up. All analyses were performed using STATA 8.0.\textsuperscript{20} Statistical significance was set at \( P<0.05 \) (two-sided).

RESULTS:

[0039] A total of 5721 asymptomatic women and 4471 referred women met the study-specific inclusion criteria, and have had their characteristics previously described.\textsuperscript{1,14,15}

Asymptomatic Population

[0040] A scatter plot and linear regression line (with the 95% confidence intervals), demonstrating the relationship between exercise capacity and age is shown
in FIG. 1, where the mean exercise capacity for age is estimated for the asymptomatic volunteer cohort. Regression analyses of exercise capacity (METs) for age was performed for the entire volunteer cohort where

\[
\text{Predicted METs} = 14.7 - 0.13(Age) \quad (1)
\]

\(n= 5721; \text{age-adjusted standard deviation} = 2.3; r= -0.51; P<0.001\)

The same regression analysis was done for the sedentary and active groups. For the active subgroup, the regression equation was

\[
\text{Predicted METs} = 17.9 - 0.16(Age). \quad (3)
\]

\(n= 866; \text{age-adjusted standard deviation} = 2.4; r= -0.59; P<0.001\)

For the sedentary subgroup, the regression equation was

\[
\text{Predicted METs} = 14.0 - 0.12(Age). \quad (4)
\]

\(n= 4643; \text{age-adjusted standard deviation} = 2.2; r= -0.49; P<0.001\)

[0041] The nomogram for the entire population (equation (1)) is shown in FIG. 2. The nomogram based on self-reported activity level (equations (3) and (4)) is shown on FIG. 3, where the active women had a greater percent predicted exercise capacity for any given age, compared to their more sedentary counterparts.

[0042] Using the regression equation (1) to predict percent normal exercise capacity for age, the percent predicted exercise capacity achieved was measured for the symptomatic and referral population. Within the asymptomatic population, those who achieved <85% age-predicted METs had a hazards ratio of death twice as great as those who achieved ≥85% age-predicted METs, \(P<0.001\).

**Referral Population**

[0043] In the referral population, the cardiac death rate increased as the ratio of observed to expected METs decreased. Similarly, death from any cause was increased as the ratio of actual to predicted METs decreased.
[0044] This study has clearly identified the mean age-predicted exercise capacity for women, as depicted by the nomogram. Although such a nomogram has been established for men and is routinely used in clinical practice, there has been no such nomogram established for women or validation of the previous findings in men in the female population. Using this large cohort of asymptomatic women from the St. James Women Take Heart Project, we have established a useful nomogram for women and validated our findings in a referral population of women. The established nomogram allows translation of exercise capacity (measured in METs) to be estimated in terms of percent predicted for any given age. An exemplary nomogram showing the percent age-predicted exercise capacity for two women, aged 60 and 30, with measured METs of 7 is shown in FIG. 4 for illustrative purposes. In both the asymptomatic and referral female cohorts, achievement of an exercise capacity less than predicted for age translates into a greater risk of all-cause mortality and cardiac mortality.

[0045] The findings in the asymptomatic cohort of women were further validated in a referral cohort of women from six different institutions. By validating the use of the nomogram that was created from an asymptomatic cohort in a referral population, we have shown that the use of a nomogram based on a normal population is appropriate and meaningful, and that all comparisons may be made to the normal population. This nomogram for healthy, volunteer women can be applied to any clinical setting where an exercise stress test is performed. Interpretation of exercise capacity as the percent predicted for age will provide a meaningful estimate of future risk of mortality in both the asymptomatic and symptomatic women.

[0046] Finally, it is noted that equation (1) is similar to an equation derived from the healthy male volunteers from the study by Morris et al., where their regression equation was

\[
\text{Predicted METs} = 14.7 - 0.11 \times (\text{Age of Man}).
\]

\[(n=244; \text{age-adjusted SD} = 2.5; r= -0.53; P<0.001)\]

In that study, the ventilatory gas exchange was measured directly during a stress test in the healthy volunteers. Both equations share the same constant in the regression
equation and the coefficient between men and women differs by 0.02. Although this number appears small at first glance, the coefficient is multiplied by age. This means that the difference in the 100% predicted exercise capacity for age between men and women will increase with age. For example, a 50-year-old male must achieve 9.2 METs to achieve 100% of the age predicted exercise capacity. In contrast, for the same aged woman, her 100% predicted exercise capacity for age would be 8.2 METs. The nomograms for men and women, when constructed side by side, demonstrate the gender difference quite easily (FIG. 5 – reproduced by permission of Dr. Victor Froelicher, MD.).
References:


20. STATA 8.0 Statistics/Data Analysis. Texas: Stata Corporation College Station.


[0047] All patents, applications, references and publications cited herein are incorporated by reference in their entirety to the same extent as if they were individually incorporated by reference.

[0048] The invention has been described with reference to various specific and illustrative embodiments. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.
CLAIMS

WHAT IS CLAIMED IS:

1. A nomogram for determining percent age-predicted exercise capacity in women, the nomogram comprising a first outer scale for measured exercise capacity, a second outer scale for age and a center scale for percent age-predicted exercise capacity, wherein the nomogram is based on a study MET levels in a group of women.

2. The nomogram of claim 1 wherein the percent age-predicted exercise capacity is calculated from a predicted exercise capacity equal to \((14.7 - 0.13 \times \text{age of woman})\), within an age-adjusted standard deviation of 2.3 and a P value < 0.001.

3. A method for determining percent age-predicted exercise capacity for a woman, the method comprising measuring the actual exercise capacity for the woman and determining the woman’s percent age-predicted exercise capacity from the nomogram of claim 1.

4. A method for determining percent age-predicted exercise capacity for a woman, the method comprising measuring the actual exercise capacity for the woman and determining the woman’s percent age-predicted exercise capacity from the nomogram of claim 2.

5. A method for determining percent age-predicted exercise capacity for a woman, the method comprising determining where a line connecting the woman’s measured exercise capacity and the woman’s age would intersect a line representing the percent age-predicted exercise capacity in a nomogram, the nomogram comprising a first outer scale for measured exercise capacity, a second outer scale for age and a center scale for percent age-predicted exercise capacity, wherein the percent age-predicted exercise capacity is calculated from a predicted exercise capacity equal to \((14.7 - 0.13 \times \text{age of woman})\), within an age-adjusted standard deviation of 2.3 and a P value < 0.001.

6. The method of claim 5 wherein the woman is asymptomatic.
7. The method of claim 5 wherein the exercise capacity is measured from a stress test selected from the group consisting of a Bruce stress test, an Ellestad stress test, a Naughton stress test and a Balke-Ware stress test.

8. A computer program product for determining percent age-predicted exercise capacity for a woman, the computer program comprising computer code adapted to determine where a line connecting the woman’s exercise capacity and the woman’s age would intersect a line representing the percent age-predicted exercise capacity in a nomogram, the nomogram comprising an outer scale for exercise capacity, an outer scale for age and a center scale for percent predicted exercise capacity, wherein the percent age-predicted exercise capacity is calculated from a exercise capacity equal to 14.7 - 0.13 x (age of woman), within an age-adjusted standard deviation of 2.3 and a P value < 0.001.

9. A computer system for determining percent age-predicted exercise capacity for a woman, the system comprising:
   (a) a central processing unit;
   (b) an input interface for transmitting the woman’s measured MET level and age to the central processing unit;
   (c) memory storing the nomogram of claim 2; and
   (d) computer code adapted to determine where a line connecting the woman’s measured exercise capacity and the woman’s age intersects the line representing the percent age-predicted exercise capacity in the nomogram.

10. The computer system of claim 9, further comprising a display unit for displaying the woman’s percent age-predicted exercise capacity.

11. An apparatus for determining percent age-predicted exercise capacity for a woman, the apparatus comprising:
   (a) the computer system of claim 9; and
   (b) an exercise platform; and
   wherein the measured MET levels are measured while the woman is using the exercise platform and the woman’s MET levels are input into the central processing unit to calculate predicted exercise capacity.
12. The apparatus of claim 11 wherein the exercise platform is a treadmill.

13. The apparatus of claim 11 wherein the exercise platform is a stepping stool.
Regression equation used for male nomogram reproduced by permission of Dr. Victor Froelicher, MD.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
   IPC(7) : A63B 21/00
   US CL : 482/8
   According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
   Minimum documentation searched (classification system followed by classification symbols)
   U.S. : 482/8
   Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>US 5,158,093 A (SHVARTZ et al) 27 October 1992, see entire document.</td>
<td>1-13</td>
</tr>
<tr>
<td>A</td>
<td>US 5,007,430 A (DARDIK) 16 April 1991, see entire document.</td>
<td>1-13</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

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Date of mailing of the international search report: 30 Jan 2006

Name and mailing address of the ISA/US
   Mail Stop PCT, Attn: ISA/US
   Commissioner for Patents
   P.O. Box 1450
   Alexandria, Virginia 22313-1450
   Facsimile No. (571) 273-3201

Authorized officer
   Glenn Richman
   Telephone No. 703 305 0858