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Lynn R. Williams

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REFERENCE VALUES FOR TOTAL BLOOD VOLUME AND CARDIAC OUTPUT IN HUMANS*

Lynn R. Williams
Associate Dean and Professor of Mathematics
Division of Liberal Arts and Sciences
Indiana University South Bend
PO Box 7111
South Bend, IN 46634

Work performed for the
Dosimetry Research Group
Health Sciences Research Division
Oak Ridge National Laboratory
Oak Ridge, Tennessee 37831

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I. INTRODUCTION

Much research has been devoted to measurement of total blood volume (TBV) and cardiac output (CO) in humans but not enough effort has been devoted to collection and reduction of results for the purpose of deriving typical or "reference" values. Identification of normal values for TBV and CO is needed not only for clinical evaluations but also for the development of biokinetic models for ultra-short-lived radionuclides used in nuclear medicine (Leggett and Williams 1989).

The purpose of this report is to offer reference values for TBV and CO, along with estimates of the associated uncertainties that arise from intra- and inter-subject variation, errors in measurement techniques, and other sources. Reference values are derived for basal supine CO and TBV in reference adult humans, and differences associated with age, sex, body size, body position, exercise, and other circumstances are discussed.

II. TOTAL BLOOD VOLUME

The analysis of TBV is based on the results of 18 original studies involving 1160 subjects (Allen et al. 1956, Berlin et al. 1951, Brady et al. 1953, Bratteby 1968, Brines et al. 1941, Brody and Nilsson 1960, Brown et al. 1962, Chien et al. 1966, Cohn and Shock 1949, Gibson and Evans 1937, Gibson et al. 1946, Moore et al. 1963, Morse et al. 1947, Nomof et al. 1954, Retzlaff et al. 1969, Schmidt et al. 1956, von Porat 1951, Wennesland et al. 1959). Measurements of TBV are based on a variety of different methods which generally require separate estimates of circulating plasma volume and the volume of the cells in the vascular space. In some studies, separate measurements of circulating plasma volume and red cell volume have been made in each subject, but more often only one of these was measured and the other was inferred using a measurement of venous hematocrit. Plasma volume studies typically use dye dilution methods or radionuclide labelling and red cell volume studies use radionuclide labelling.

There are two potential sources of error when the venous hematocrit is used to estimate TBV: (1) the measured venous hematocrit generally overestimates actual venous hematocrit due to the less than perfect packing of cells by the centrifuge and (2) the venous hematocrit is larger than the whole body hematocrit. Variation in technique can lead to different fractions of plasma trapped in the red cell column of centrifuged blood (reported range 2-8% in Chaplin and Mollison 1952), but several investigators (Brady et al. 1953, Chien et al. 1966, Cohn and Shock 1949, Nadler and Hidalgo 1965, Schmidt et al. 1956) multiplied measured hematocrit by 0.96 to obtain a corrected hematocrit. Over a wide range of body hematocrit the average ratio of whole body hematocrit to corrected venous hematocrit is nearly constant with a value of 0.91 in normal humans (reported range 0.87-0.92, Chaplin et al. 1953, Nadler and Hidalgo 1965, Retzlaff et al. 1969). In this review, these same correction factors (0.96 and 0.91) were applied to adjust published TBV values from studies not using correction factors. Studies of TBV not using correction factors and not reporting individual hematocrit values were not used in the analysis of TBV.

Data on TBV are summarized in Table 1 and suggested reference TBV values for a given age are presented in Table 2. Trimmed means were computed by dropping the highest 20% and the lowest 20% of study values in each age range and computing a mean for the remaining middle 60% of the study values. Most measurements of human TBV have been on young adults, usually males. Two studies (Brines et al. 1941, Morse et al. 1947) were conducted on infants and children, and two

Table 1. Summary of reported values of blood volume within age groups.

Blood Volume (L)								
	Males				Females			
Age range (y)	mean	s.d.	number	trimmed mean	mean	s.d.	number	trimmed mean
0.00-0.05	0.27*	0.1	45	0.27*	0.27*	0.1	41	0.27*
0.4 - 0.8	0.45	0.1	5	0.41				
1.1 - 2.2	0.88	0.1	3		0.69	0.1	3	
2.8 - 4.9	1.23	0.2	3		1.01	0.2	9	1.01
5.0 - 7.1	1.56	0.4	6	1.47	1.44	0.3	2	
7.5 - 9.9	2.11	0.4	11	2.06	1.80	0.4	7	1.75
10 - 12	2.66	0.5	16	2.67	2.10	0.4	7	2.13
13 - 15	4.34	1.0	34	3.95	3.28	0.5	7	3.28
16 - 19	5.03	0.9	28	5.05	3.43	0.5	11	3.39
20 - 29	5.28	0.8	303	5.24	3.88	0.6	137	3.88
30 - 39	5.12	0.7	143	5.09	4.09	0.6	62	4.05
40 - 49	5.34	0.8	69	5.30	3.86	0.6	27	3.81
50 - 59	5.06	0.9	28	5.03	3.76	0.7	20	3.66
60 - 69	4.92	0.8	30	4.83	3.81	0.8	6	3.68
70 - 79	4.62	0.7	52	4.57	3.63	0.7	43	3.50
80 - 83	4.39	0.5	24	4.36	3.48	0.6	17	3.52

*Values for males and females were combined in this age group.

Table 2. Suggested reference values for blood volume.

Age (y)	Blood Volume (L)			
	Males		Females	
	mean	s. d.	mean	s. d.
0	0.27	0.1	0.27	0.1
0.5	0.4	0.1	0.4	0.1
2	0.8	0.2	0.7	0.2
5	1.4	0.3	1.2	0.3
10	2.4	0.5	2.0	0.4
15	4.5	1.0	3.3	0.5
24	5.3	0.9	3.9	0.6
34	5.3	0.9	4.0	0.6
44	5.3	0.9	3.9	0.6
54	5.1	0.9	3.8	0.7
64	4.8	0.8	3.7	0.7
74	4.6	0.8	3.5	0.7

studies (Bratteby 1968, Brody and Nilsson 1960) used newborns. Blood volume measurements are typically made with the subject in the recumbent position and there is a slight decrease in circulating plasma volume, and hence TBV, when the subject moves from the horizontal to the upright position (Hagan et al. 1978, Lehtovirta et al. 1972). Values in Tables 1 and 2 represent recumbent TBV.

Various authors (Allen et al. 1956, Bratteby 1968, Brown et al. 1962, Chien et al. 1966, Cropp 1971, Inkley et al. 1955, Morse et al. 1947, Retzlaff et al. 1969, Strandell 1964, von Porat 1951, Wennesland et al. 1959) have used multi-linear regression to investigate the relationships between TBV and one or more functions of height, weight, age, or body surface area (BSA), but these regressions were based on relatively small data sets. Analyses of the combined data were performed separately for males and females except newborns, for which sex generally was not reported. The data for males and females were separated into additional categories based on the age and weight of the subject: females under 40 kg and 13 y, males under 45 kg and 14 y, females over 40 kg and 13 y, and males over 45 kg and 14 y. There are several reasons for looking at subsets of the data: (1) the relationships between TBV and age or weight appear linear but the slopes seem to be different for children than for adults; (2) the relationship between TBV and age in children is different from the relationship in adults; and (3) there are fewer data points and there is less variation in TBV in the lower weight and age groups. The data are insufficient to draw meaningful conclusions for adult females whose weight lies outside the 40-80 kg range or adult males whose weight lies outside the 45-100 kg range.

Reference TBVs for young children of a given sex, weight, and age can be obtained from one of the least squares regressions given below. In each category, an attempt was made to determine the regression variables with nonzero coefficients (p value < 0.01) which appeared to satisfy the regression assumptions and yielded the equation with the highest correlation coefficient. For newborns (41 subjects), the linear least squares regression of TBV on weight yields

$$\text{TBV (L)} = 0.0875 \times \text{weight (kg)}$$

with $r^2 = 0.98$. For female children (30 subjects aged 1 w to 12.5 y), the multiple linear regression of TBV on weight and age yields

$$\text{TBV (L)} = 0.2263 + 0.0326 \times \text{weight (kg)} + 0.0784 \times \text{age (y)}$$

with $r^2 = 0.90$. The corresponding multiple linear regression equation for male children (57 subjects aged 3 w to 13.9 y) is

$$\text{TBV (L)} = 0.0393 \times \text{weight (kg)} + 0.1299 \times \text{age (y)}$$

with $r^2 = 0.98$.

Height has been used as a predictor variable in several published regression equations involving TBV (Brown et al. 1962, Chien et al. 1966, Morse et al. 1947, Retzlaff et al. 1969, Strandell 1964, von Porat 1951, Wennesland et al. 1959). Weight and the cube of height, used as dependent variables (Allen et al. 1956) to predict TBV in adults, seem to yield better regression equations of TBV than linear equations using combinations of weight, age, or BSA. A nonlinear least squares regression was attempted using the more general model

$$\text{TBV} = a + b \times \text{weight} + c \times \text{height}^d,$$

where a, b, c and d are constants. The nonlinear regression using post-adolescent females (296 subjects aged 13 y or older) yields

$$\text{TBV (L)} = 0.7716 + 0.0343 \times \text{weight (kg)} + 0.1385 \times [\text{height (m)}]^{4.257},$$

with $r^2 = 0.52$. The corresponding equation for males (677 subjects aged 14 y or older) is

$$\text{TBV (L)} = 1.6832 + 0.0299 \times \text{weight (kg)} + 0.0849 \times [\text{height (m)}]^{4.953},$$

with $r^2 = 0.59$. These equations do not appear to improve multiple linear regressions using weight and the cube of height or using weight and height; the corresponding r^2 values are the same to two decimal places. Regression equations for post-adolescent females are

$$\text{TBV (L)} = 0.3394 + 0.0343 \times \text{weight (kg)} + 0.3574 \times [\text{height (m)}]^3$$

and

$$\text{TBV (L)} = -2.4854 + 0.0346 \times \text{weight (kg)} + 0.0268 \times \text{height (cm)}.$$

The corresponding equations for males are

$$\text{TBV (L)} = 0.8278 + 0.0297 \times \text{weight (kg)} + 0.4183 \times [\text{height (m)}]^3$$

and

$$\text{TBV (L)} = -3.4722 + 0.0298 \times \text{weight (kg)} + 0.0374 \times \text{height (cm)}.$$

III. CARDIAC OUTPUT AND CARDIAC INDEX

Although there has been considerable debate concerning the proper method of standardization of CO with respect to body parameters, the most common method is the cardiac index (CI), which is defined to be the quotient of CO (L/min) and BSA (m^2). The original reason for using CI as the method of standardization was that the human basal metabolic rate is expressed in terms of surface area and basal CO is expected to be directly related to the basal metabolic rate (Guyton et al. 1973).

Many investigators have suggested that a multiple regression of CO on several variables such as height, weight, or age would be more appropriate than using BSA as the standard for comparison. Krovetz and Goldbloom (1972), using data on 115 normal subjects 1 month to 20 years of age, concluded that height was a better predictor of CO than BSA and found that height had a slightly higher correlation coefficient. Guyton et al. (1973) suggested $(\text{weight})^{0.75}$ as a standard based on results of animal studies. An analysis of published data on CO in normal individuals would seem to indicate that no single method of standardization with respect to body size will yield comparable values for a 'standardized cardiac output' for both sexes over the entire age range. However, since CI is widely used to express cardiac output, reference values are presented for both CO and CI.

Although there are a variety of invasive and non-invasive methods available for measuring CO, attention here is restricted to studies using either direct Fick or indicator dilution techniques. Non-invasive procedures such as the Doppler method, radionuclide injections, impedance cardiography, or echocardiography are not yet considered to be sufficiently reliable to be used to determine reference values (Conway 1990). Invasive procedures used to determine CO involve either the Fick principle, dye-dilution, or thermodilution. Studies that compare Fick or dye-dilution estimates of CO with thermodilution estimates generally show a high positive correlation with r^2 ranging from 0.70 to 0.99 (Kadota 1985, Riedinger and Shellock 1984), but other studies have shown that thermodilution can substantially overestimate dye-dilution determined CO (de Leeuw and Birkenhäger 1990, Russell et al. 1990). For these reasons, reference values for supine resting CO are based on studies providing individual values for each subject and using either the Fick principle or dye-dilution (Adams and Lind 1957, Anthonisen and Crone 1959, Barratt-Boyes and Wood 1957 1958, Bevegard et al. 1966, Bickelmann et al. 1963, Bing et al. 1950, Bolomey et al. 1949, Brotmacher and Fleming 1957, Cayler et al. 1963, Chapman et al. 1950, Chapman and Fraser 1954a 1954b,

Cournand et al. 1945, Donald et al. 1953 1955 1957, Doyle et al. 1951, Ebert et al. 1949, Emmanouilides et al. 1970, Etsten and Li 1954 1955, Freedman et al. 1955, Fries et al. 1952, Gessner et al. 1965, Granath and Strandell 1964, Granath et al. 1964, Grimby et al. 1966, Hamilton et al. 1948, Holmgren el al. 1960, Kattus et al. 1955, Kennedy et al. 1966, Kowalski et al. 1954, Levine et al. 1962, Levinson et al. 1966, Lucas et al. 1961, McGregor et al. 1961, Muiesan et al. 1968, Myers 1947, Norryd et al. 1974, Nylin et al. 1961, Reeves et al. 1961a 1961b, Regan et al. 1961, Riley et al. 1948, Ross et al. 1966, Rotta et al. 1956, Schnabel et al. 1959, Shaver et al. 1968, Shepherd et al. 1955, Slonim et al. 1954, Sproul and Simpson 1964, Stead et al. 1945, Stenberg et al. 1967, Thomas et al. 1962, Thomasson 1957, Werko et al. 1949).

A. Cardiac Output

Summary statistics of CO data for studies that enumerated values for individual subjects are presented in Table 3. The trimmed means were computed by taking the average of the values that remained after the highest 20% and lowest 20% of the values were deleted in each age range. The standard deviations of the individual values were computed using all the available data.

Over the entire age range (1 d to 85 y), the correlation in each sex category between CO and any one of the variables weight, height, or BSA is greater than 0.6. The correlation between CO and BSA is roughly the same as that for either of the other variables including $(\text{weight})^{0.75}$.

A multiple linear regression analysis over the entire age range is not appropriate because there is a strong nonlinear relationship between CO and age. The nonlinearity is particularly evident when CO is standardized with respect to a measure of body size such as BSA or height. In age subintervals for adults on which the relationships between CO and other variables appear to be linear (age 20-60 y), the individual variation in CO appears to be much greater that the variation that can be explained by a measure of body size. For adult males, BSA and age appear to be better predictors of CO than linear combinations of age, weight, or height, and for females for which all variables (age, weight, height, and BSA) were reported, BSA appears to be the best predictor. However, for either sex type, less than five percent of the total variation in adult CO is explained by the regression. The linear least squares regression using 415 males aged 20 to 60 y gives

$$\text{CO (L/min)} = 4.067 + [1.665 \times \text{BSA (m}^2)] - [0.017 \times \text{Age (y)}]$$

with $r^2 = 0.05$. The regression using 143 females aged 20 to 60 y gives

$$\text{CO (L/min)} = 3.396 + [1.565 \times \text{BSA (m}^2)]$$

with $r^2 = 0.02$.

Table 3. Summary of reported values of cardiac output within age groups, computed using either direct Fick or indicator dilution techniques.

Age range (y)	Males				Females			
	mean	s.d.	number	trimmed mean	mean	s.d.	number	trimmed mean
0.00-0.02	0.57*	0.2	46	0.56*	0.57*	0.2	46	0.56*
0.04-0.40	0.75*	0.3	6	0.73*	0.75*	0.3	6	0.73*
0.6 - 1.0	1.14*	0.2	2		1.14*	0.2	2	
1.7 - 4.0	2.47*	0.8	6	2.39*	2.47*	0.8	6	2.39*
5.0 - 7.0	3.85*	1.1	22	3.69*	3.85*	1.1	22	3.69*
8.0 - 9.5	4.70*	1.4	16	4.57*	4.70*	1.4	16	4.57*
10 - 12	4.96	0.9	5	4.63	4.92	1.2	14	4.82
13 - 15	5.93	1.6	11	6.07	6.01	1.1	3	
16 - 19	6.64	1.5	46	6.64	6.33	1.4	17	6.21
20 - 29	6.98	1.5	170	6.92	6.04	1.6	71	5.91
30 - 39	6.53	1.7	121	6.41	5.63	1.3	34	5.54
40 - 49	6.31	1.4	84	6.25	5.95	1.3	25	5.94
50 - 59	6.42	1.5	42	6.33	6.51	1.5	11	6.40
60 - 69	5.89	1.5	26	5.73	5.36	1.8	11	5.17
70 - 79	5.79	0.9	11	5.74				
80 - 83	5.15	0.4	2					

*Values for males and females were combined in these age groups.

The situation is somewhat different for children. For newborns, none of the regressions of CO on weight, height or BSA are significant. For children age 0.2 to 4 y (10 subjects), no studies reporting both CO and height or weight were found. Linear least squares regressions of CO on age or BSA seem appropriate:

$$CO\ (L/min) = 0.734 + [0.563 \times Age\ (y)]$$

with $r^2 = 0.75$ and

$$CO\ (L/min) = -0.514 + [5.223 \times BSA\ (m^2)]$$

with $r^2 = 0.61$.

For older children (age 5 to 19 y) a nonlinear regression was attempted on the combined sex groups using weight as the predictor. The corrected r^2 is 0.81 and the regression equation is

$$CO\ (L/min) = 3.107 + \{0.012 \times [Weight\ (kg)]^{1.369}\}.$$

Some of the criticisms of BSA as a method of CO standardization stem from the fact that BSA is generally not measured but rather estimated as a nonlinear function of height and weight (or other easily measured variables). Such methods do not take into account the difference in body contours among the sexes and they tend to underestimate BSA in children and adult males and overestimate BSA in adult females (Krovetz 1965). For children, standardization with respect to BSA, weight, height, or age can be quite useful in predicting CO. In adults little is to be gained by standardization with respect to a measure of body size except for the fact that the division of CO by BSA (or estimated BSA) does appear to provide comparable distributions of values at a given age in the two sex types.

B. Cardiac Index

Summary statistics of CI data for studies that enumerated values for individual subjects are presented in Table 4. For studies that provided CO, height, and weight for each individual, BSA was estimated using the equations of Gehan and George (1970). Trimmed means and standard deviations were computed as described above for CO.

A number of researchers (Brandfonbrener et al. 1955, Cournand et al. 1945, Granath and Strandell 1964, Jegier et al. 1963, Julius et al. 1967, Katori 1979, Krovetz and Goldbloom 1972, Kuikka and Lansimies 1982, Lammerant et al. 1961, Luisada et al. 1980) measured CI of individuals to investigate the relationship between CI and age. Although there is substantial quantitative variation in the results, most researchers observed either a linear or nonlinear decrease in CI with age. Although some of the disparate findings can be ascribed to the difference in technique, much

Table 4. Summary of reported values of cardiac index within age groups, computed using either direct Fick or indicator dilution techniques.

Age range (y)	Males			Females			Males and Females	
	mean	s.d.	number	mean	s.d.	number	trimmed mean	number
0.00-0.02	2.91	0.9	16	2.90	1.0	16	2.81	46
0.04-0.40				2.76		1	3.58	6
0.6 - 1.0							3.20	2
1.7 - 4.0							4.40	6
5.0 - 7.0	4.30	0.6	5	4.70	1.4	7	4.52	22
8.0 - 9.5	4.58	1.0	7	4.86	1.1	3	4.57	16
10 - 12	4.98	1.1	5	4.36	1.2	14	4.63	25
13 - 15	3.56	1.0	11	4.13	0.5	3	4.06	21
16 - 19	3.75	0.9	46	4.03	0.8	17	3.80	67
20 - 29	3.71	0.8	170	3.77	1.1	71	3.68	260
30 - 39	3.46	0.9	121	3.56	0.7	34	3.43	170
40 - 49	3.43	0.7	84	3.70	0.8	25	3.43	119
50 - 59	3.55	0.8	42	4.08	1.0	11	3.58	58
60 - 69	3.19	0.8	26	3.18	0.9	11	3.16	38
70 - 79	3.11	0.5	11				3.08	12
80 - 83	2.99	0.1	2					

of the diversity is due to the variation in basal CO among similar individuals and even the variation possible in the values of a single individual. Studies that considered large numbers of individuals at several different ages suffered from the fact that there were too few individuals in any small age interval. Also, the studies that included adults have few if any values for the young child. By looking at three studies, Prec and Cassels (1955) for infants, Brotmacher and Fleming (1957) for youths, and Brandfonbrener et al. (1955) for adults, Guyton et al. (1973) gave a curve which provides the approximate shape of the average male CI as a function of age. There is a sharp increase in the average CI until the age of 4 or 5 y with a leveling off until around the age of 10 or 11 y. The average CI falls sharply during the teen years followed by more gradual decreases from age 20 y to age 60 y, and there is another more rapid decrease at about age 60 y.

There does not appear to be a difference in the male and female average CI values at a given age except possibly for those years around the fifth decade of life. There is a significant difference between the average male and average female CI values in both the 40-49 y and 50-59 y age groups (p-values 0.06 and 0.03 respectively using two-sample t-tests). The nonparametric Kolmogorov-Smirnov two-sample test also indicates a significant difference in the male and female CI distributions in the 50-59 y age group. None of the other intervals have male and female CI averages which appear to be significantly different, although individual information for the first few years of life is sparse. The individual values of female CI indicate that there may be an increase in the female CI in the 40-60 y age range, but the sample size is small and neither of the earlier mentioned parametric or nonparametric tests indicate significant differences in the female CI values during the third, fourth and fifth decades of life. Furthermore, longitudinal studies of Katori (1979), Kuikka and Lansimies (1982) and Luisada et al. (1980) do not indicate an increase in female CI with age during adulthood. It may be that the observed increase in the trimmed mean adult female CI is due to random fluctuations in the data.

C. Reference Values for CO and CI

Table 5 contains suggested reference values for CO and CI as a function of age and sex. Reference values for male and female CI through age 40 y are based on the trimmed mean CI that was computed using all available data. Because of the possible sex difference near the fifth decade of life, male reference values for higher ages are based on the trimmed mean CI for males. It is assumed that the average female CI remains relatively constant throughout the 35-55 y age range. The data is inadequate to make reliable statements about the average female CI for older adults.

Table 5. Suggested reference values for cardiac output and cardiac index.

Age (y)	Cardiac Output ($L \cdot min^{-1}$)				Cardiac Index ($L \cdot min^{-1} \cdot m^{-2}$)			
	Males		Females		Males		Females	
	mean	s.d.	mean	s.d.	mean	s.d.	mean	s.d.
0	0.6	0.2	0.6	0.2	2.8	0.9	2.8	0.9
1	1.2	0.4	1.2	0.4	3.6	0.9	3.6	0.9
3	2.5	0.9	2.5	0.9	4.3	1.3	4.3	1.3
6	3.9	1.1	3.9	1.1	4.5	1.3	4.5	1.3
10	5.0	1.3	5.0	1.3	4.6	1.3	4.6	1.3
14	6.0	1.5	6.0	1.4	4.1	1.3	4.1	1.3
18	6.6	1.5	6.3	1.4	3.8	1.0	3.8	1.0
24	7.0	1.5	6.0	1.4	3.7	0.9	3.7	0.9
34	6.5	1.5	5.9	1.4	3.6	0.9	3.6	0.9
44	6.4	1.5	5.9	1.4	3.5	0.8	3.6	0.9
54	6.4	1.5	5.9	1.4	3.4	0.8	3.6	0.9
64	5.9	1.5			3.2	0.7		
74	5.8	1.4			3.1	0.7		

Reference values for CO are assumed to be independent of sex until near age 10 y. Reference values for female CO are based on the trimmed mean CO for females through age 35 y. The average female CO from age 35 y to 55 y is assumed to be relatively constant. The individual data values for CI and CO as a function of age are compared with reference curves for each sex in Figures 1-4; curves representing one standard deviation from the reference curve are also included. The reference curves for male and female CI are compared with reference curves suggested by data of other authors in Figures 5 and 6. Most of the longitudinal studies depicted in Figures 5 and 6 (Kuikka and Lansimies 1982, Lammerant et al. 1961, Luisada et al. 1980) used methods other than direct Fick or dye-injection for measuring CO.

D. Cardiac output and body position

Although most of the CO studies reported in the literature contain values of CO measured with the subject recumbent, several researchers have considered the effect on CO of movement to a position other than the horizontal position (Bevegard et al. 1966, Boer et al. 1979, Donald et al. 1953, Gilmore et al. 1952, Granath et al. 1961, Granath et al. 1964, Grimby et al. 1966, Hanson et al. 1968, Hartley et al. 1969, Julius et al. 1967, Lehtovirta et al. 1972, Levinson et al. 1966, McGregor et al. 1961, McMichael and Sharpey-Schafer 1944, Murata et al. 1981, Ohlsson et al. 1983, Pyorala 1966, Rankin et al. 1975, Reeves et al. 1961a, Segel et al. 1973, Smith et al. 1970, Stead et al. 1945, Stenberg et al. 1967, Tuckman and Shillingford 1966, Wang et al. 1960, Weissler et al. 1957). All the studies report an average decrease in the CO associated with a movement away from horizontal, even though there were some individual exceptions (possibly due to change in anxiety level). In some of the studies, the subjects were strapped to a table which could be rotated to give various degrees of tilt away from horizontal; other studies considered the effect of movement from a horizontal position to a sitting or standing position. It appears that the resting CO peaks at the horizontal position.

The weighted average (weighted by the number of subjects) decrease in CO is 18% (range of 5% to 30%) when the subject moves from the horizontal to a seated position (Bevegard et al. 1966, Donald et al. 1953, Granath et al. 1961, Granath et al. 1964, Grimby et al. 1966, Hartley et al. 1969, Julius et al. 1967, McGregor et al. 1961, Ohlsson et al. 1983, Stenberg et al. 1967). The average decrease is 23% (range of 16% to 38%) when the subject moves from the horizontal to a standing position (Hanson et al. 1968, McMichael and Sharpey-Schafer 1944, Reeves et al. 1961a, Wang et al. 1960).

Figure 1. Age related changes in male supine cardiac output are depicted. Individual measurements are compared to the suggested reference curve (solid line) and curves that lie one standard deviation away from the reference curve (dotted lines).

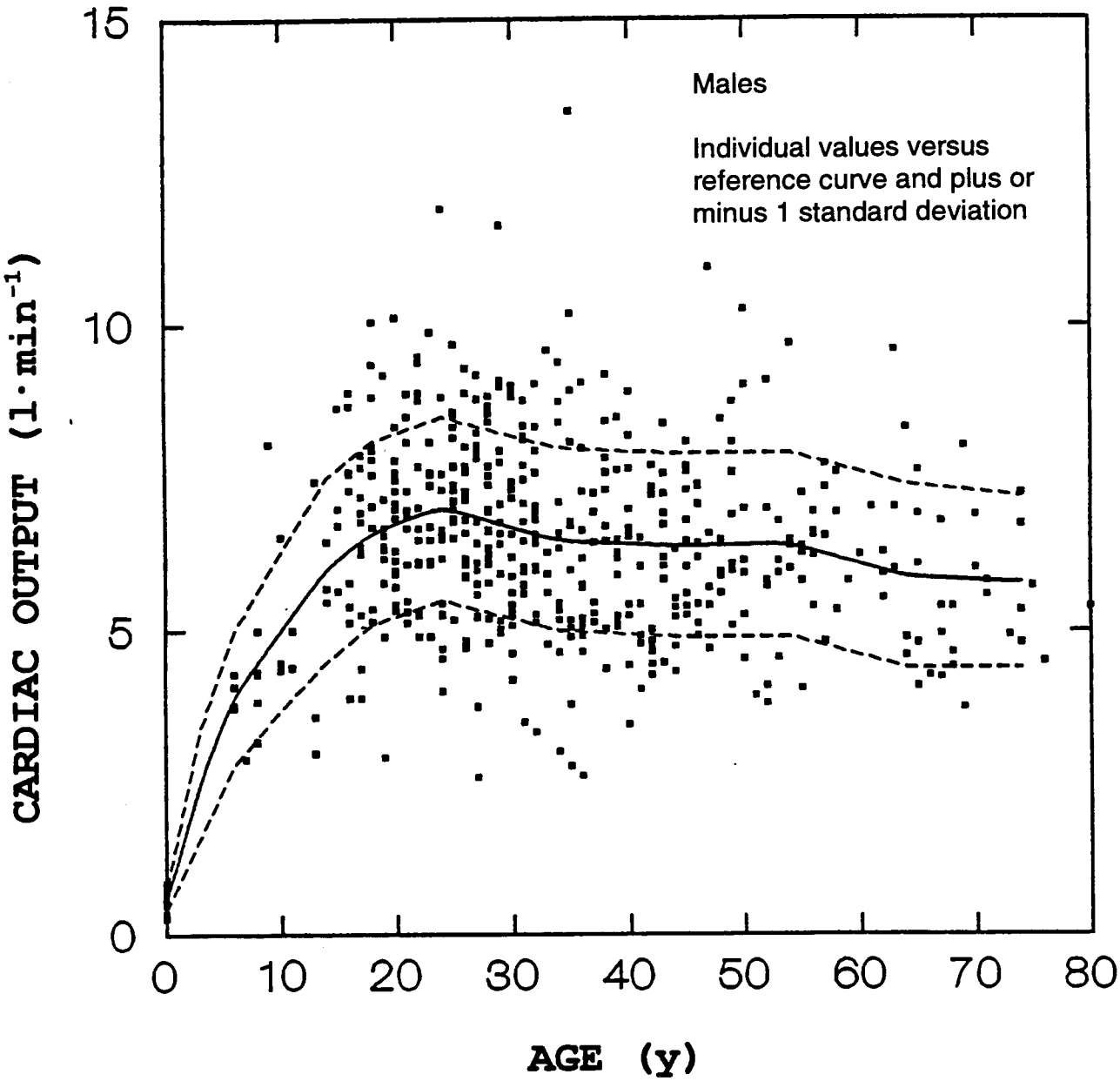


Figure 2. Age related changes in female supine cardiac output are depicted. Individual measurements are compared to the suggested reference curve (solid line) and curves that lie one standard deviation away from the reference curve (dotted lines).

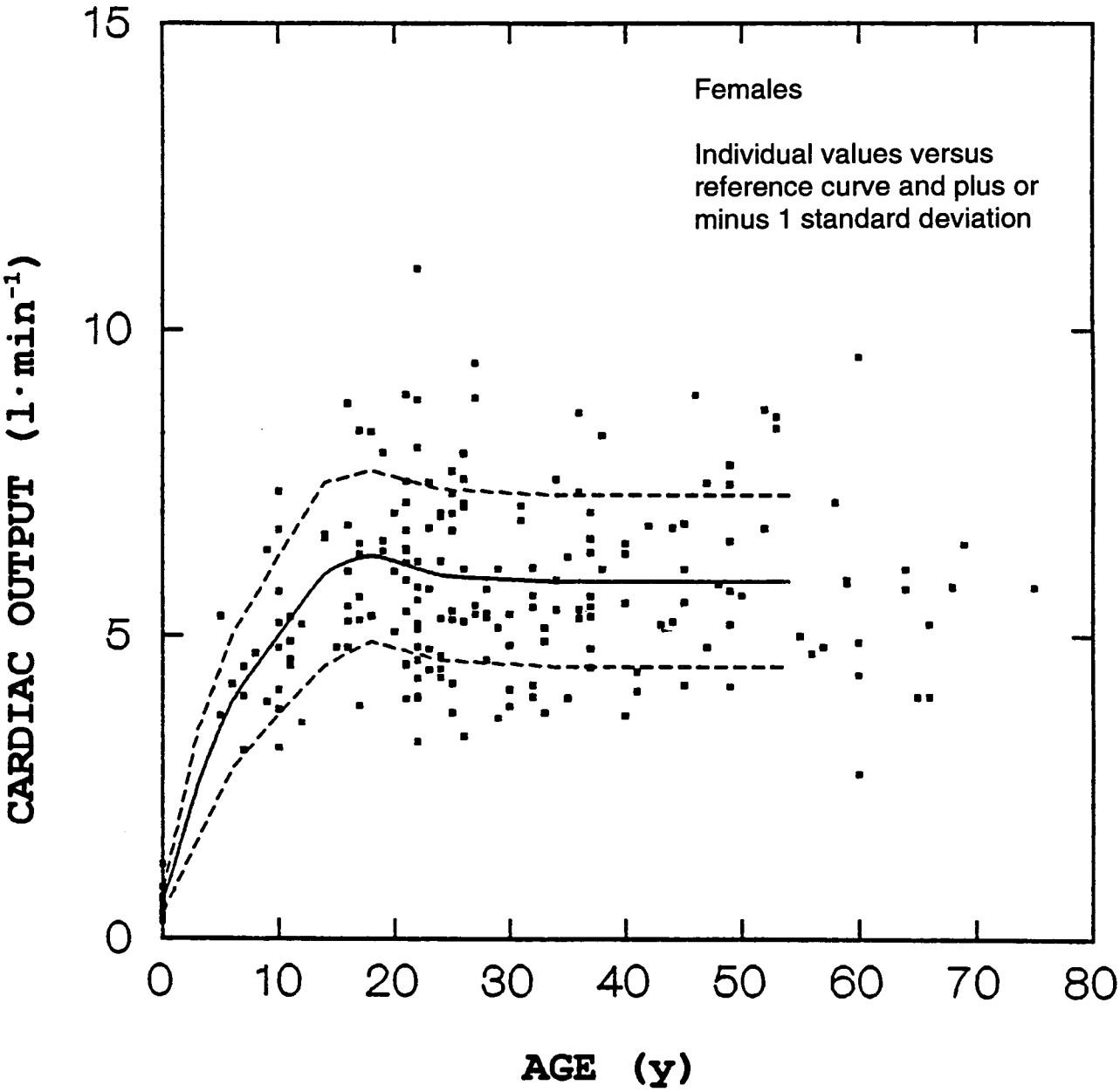


Figure 3. Age related changes in male supine cardiac index are depicted. Individual measurements are compared to the suggested reference curve (solid line) and curves that lie one standard deviation away from the reference curve (dotted lines).

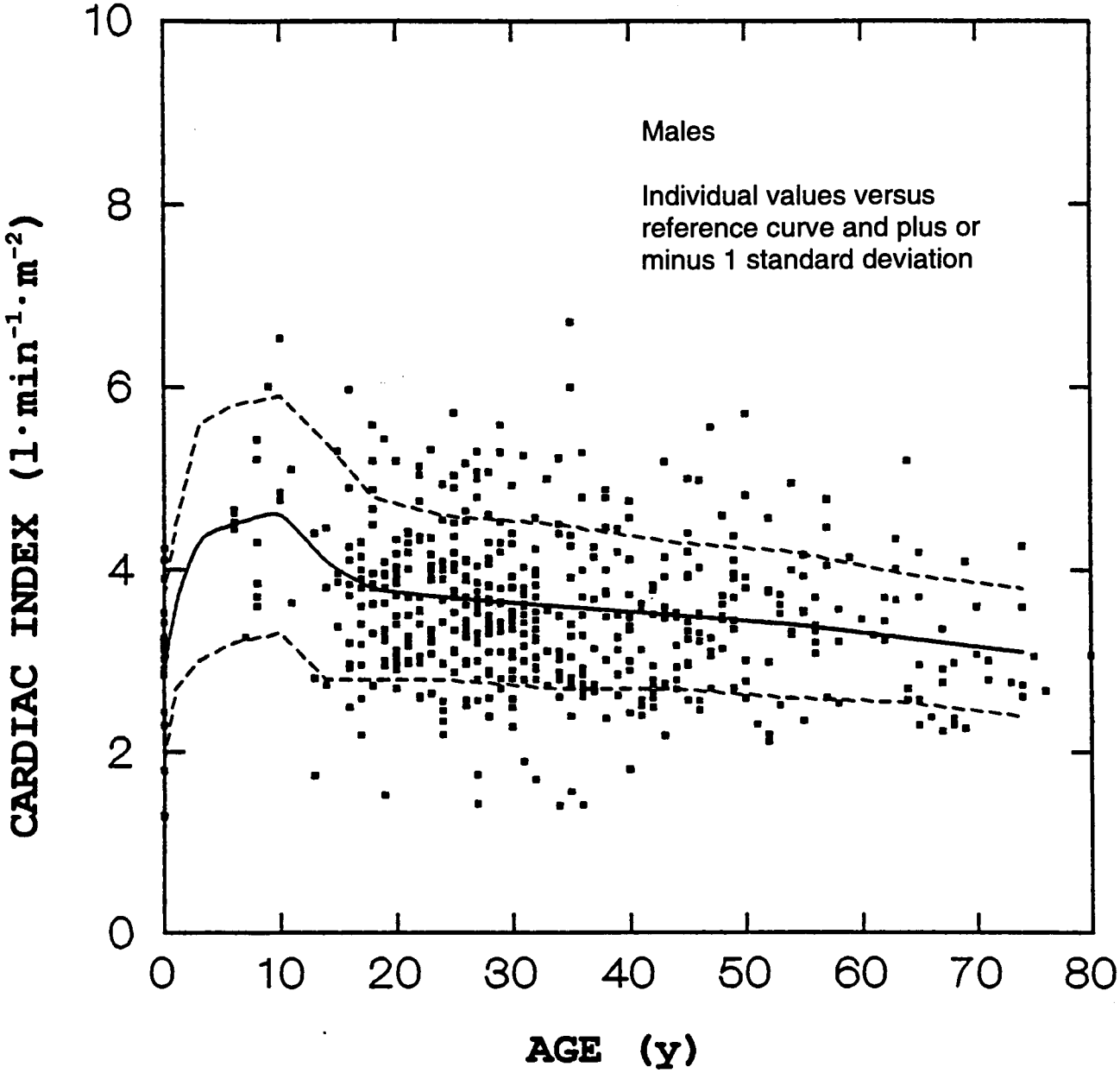


Figure 4. Age related changes in female supine cardiac index are depicted. Individual measurements are compared to the suggested reference curve (solid line) and curves that lie one standard deviation away from the reference curve (dotted lines).

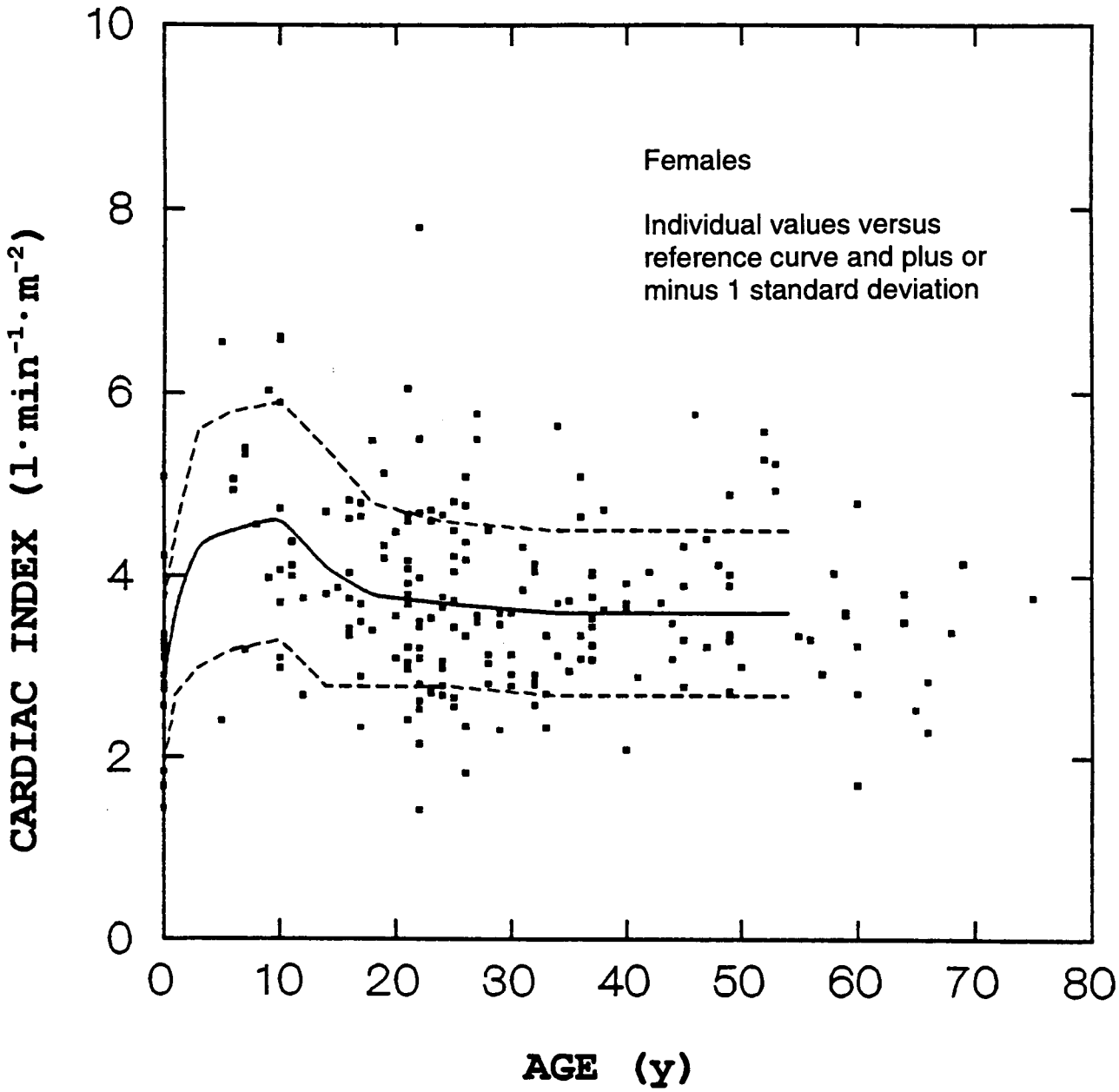


Figure 5. The suggested reference curve (solid line) for male supine cardiac index is compared to curves based on average values from studies on subjects in several different age groups.

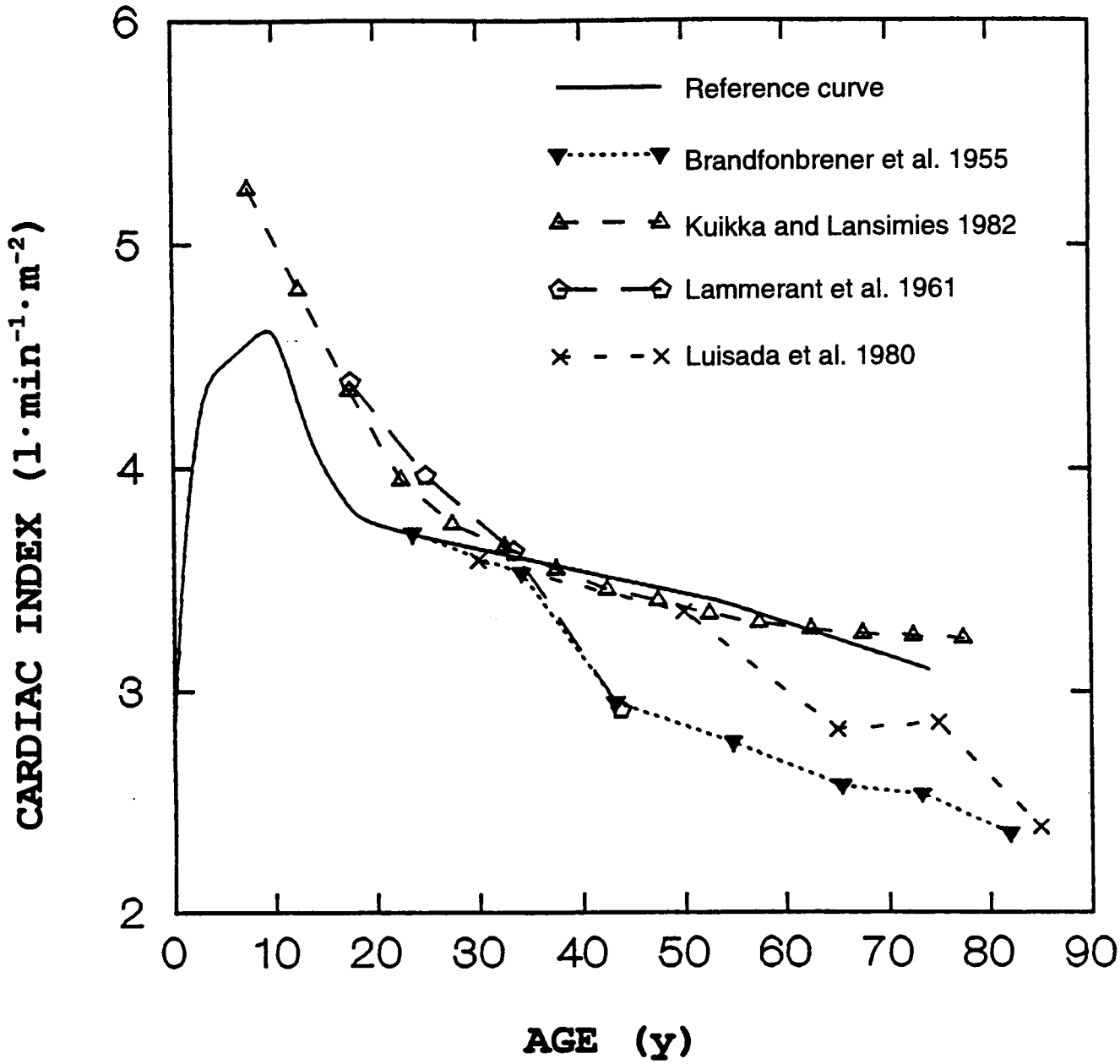
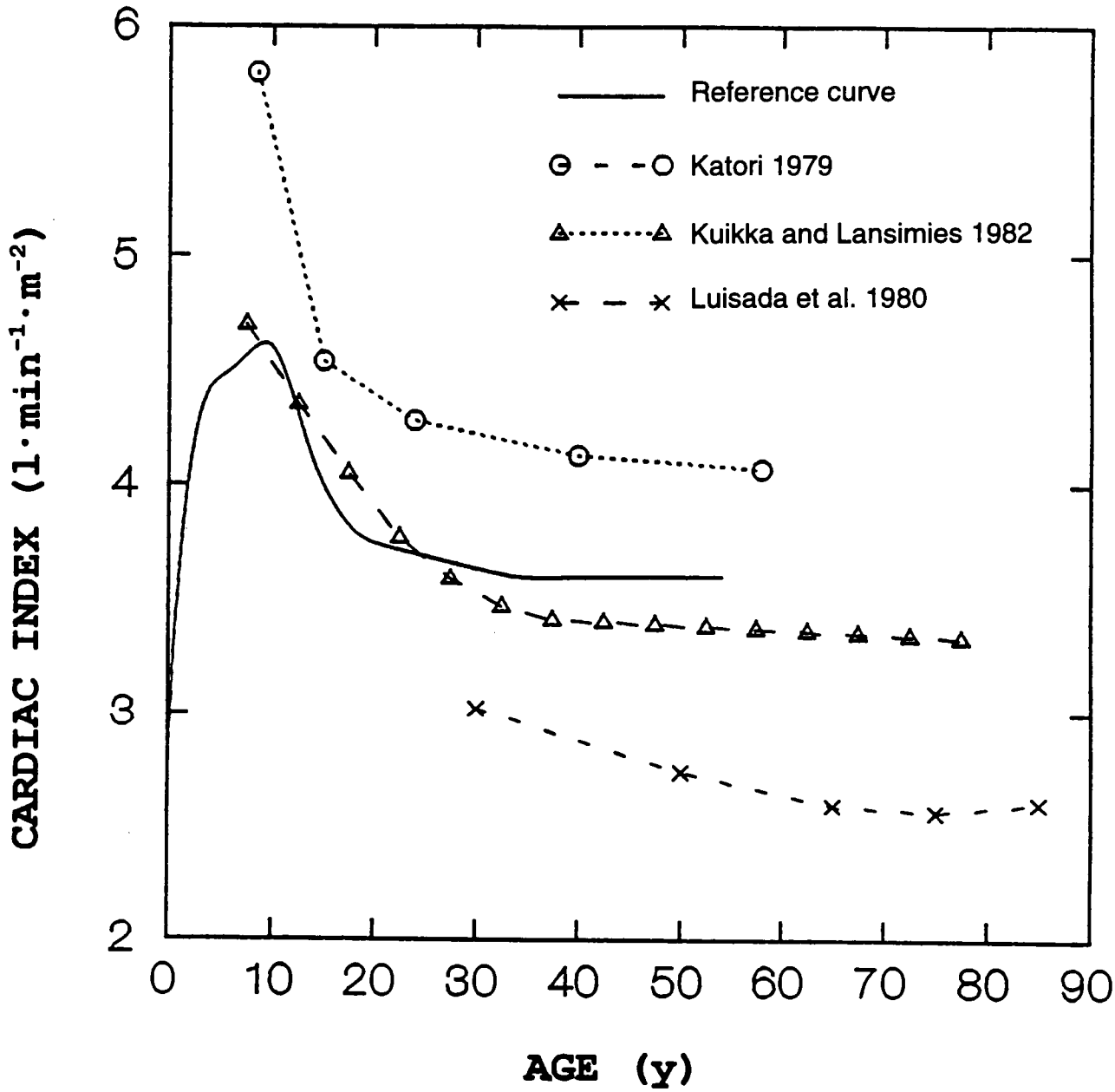


Figure 6. The suggested reference curve (solid line) for female supine cardiac index is compared to curves based on average values from studies on subjects in several different age groups.



The results from studies which rotated the subjects through various degrees of tilt are reported in Table 6. A tilt of as much as 10 degrees away from the horizontal will apparently decrease the CO by approximately 5%, and a tilt of 20 to 30 degrees produces a CO similar to the seated value. The decrease in CO when the subject is tilted by 45 degrees or more is comparable to the decrease caused by standing.

E. Cardiac output and exercise

Cardiac output increases dramatically in response to heavy exercise. At higher levels of oxygen uptake, a unit increase in oxygen uptake produces a smaller increase in CO than that produced at lower levels of oxygen uptake. However, the relationship between oxygen uptake and CO appears to be approximately linear if attention is restricted to certain subintervals of oxygen uptake values.

Regressions of CO (L/min) or CI (L/min/m^2) on oxygen uptake (L/min) were obtained from studies that reported individual values and used direct Fick or indicator dilution techniques (Astrand et al. 1964, Barratt-Boyes and Wood 1957, Donald et al. 1955 1957, Ekblom et al. 1968, Freedman et al. 1955, Holmgren et al. 1960, Klausen 1966, Kowalski et al. 1954, Levine et al. 1962, Reeves et al. 1961a 1961b, Riley et al. 1948, Ross et al. 1966, Tabakin et al. 1964). The assumptions of linear regression appear to be met if attention is restricted to oxygen uptake values less than 0.7 L/min or if attention is restricted to oxygen uptake values greater than 0.7 L/min (see Figures 7-11), but the slopes of the relationships are clearly different on these two intervals. Male and female values can be combined in all the regressions except for CO and oxygen uptake at low work levels.

The linear least squares regression of CO on oxygen uptake for males (226 data pairs) yields

$$CO\ (L/min) = 4.0 + 10 \times VO_2\ (L/min) \quad (VO_2 \leq 0.7\ L/min)$$

with $r^2 = 0.35$. For females (104 data pairs), the corresponding regression is $CO\ (L/min) = 4.1 + 8.4 \times VO_2\ (L/min) \quad (VO_2 \leq 0.7\ L/min)$

with $r^2 = 0.51$. The corresponding regression of CI for males and females (330 data pairs) yields

$$CI\ (L/min/m^2) = 2.4 + 5.1 \times VO_2\ (L/min) \quad (VO_2 \leq 0.7\ L/min)$$

with $r^2 = 0.37$. For the 358 data pairs involving male and female CO and CI at higher values of oxygen uptake, the regressions yield

$$CO\ (L/min) = 7.0 + 4.7 \times VO_2\ (L/min) \quad (VO_2 > 0.7\ L/min)$$

with $r^2 = 0.78$ and

$$CI\ (L/min/m^2) = 4.0 + 2.3 \times VO_2\ (L/min) \quad (VO_2 > 0.7\ L/min)$$

with $r^2 = 0.72$.

Table 6. Average decrease in cardiac output induced by a rotation away from a horizontal position.

Age range (y)		Number of subjects	decrease (%)	Degrees from horizontal	Reference
lower	upper				
40	53	4	3	10	Tuckman and Shillingford 1966
18	29	4	7	10	Tuckman and Shillingford 1966
16	25	2	10	20	Tuckman and Shillingford 1966
35	50	6	19	20	Tuckman and Shillingford 1966
--	--	5	25	20	Boer et al. 1979
22	39	4	5	30	Segel et al. 1973
23	23	1	19	30	Tuckman and Shillingford 1966
37	71	5	19	30	Tuckman and Shillingford 1966
30	40	3	19	40	Tuckman and Shillingford 1966
26	62	20	20	35	Murata et al. 1981
50	61	5	21	45	Gilmore et al. 1952
30	33	2	34	45	Gilmore et al. 1952
22	38	3	22	55	Tuckman and Shillingford 1966
18	25	2	8	60	Weissler et al. 1957
31	42	3	17	60	Tuckman and Shillingford 1966
22	39	4	24	60	Segel et al. 1973
20	32	30	15	70	Lehtovirta et al. 1972
26	62	20	25	70	Murata et al. 1981
20	36	12	27	70	Pyorala 1966
20	26	8	18	70	Smith et al. 1970
--	--	5	24	70	Stead et al. 1945
20	35	10	30	75	Rankin et al. 1975
23	37	8	13	90	Loeppky et al. 1981
22	39	4	64	90	Segel et al. 1973

Figure 7. The regression line for cardiac output as a function of oxygen uptake is compared to individual male values with VO_2 values less than or equal to 0.7 $l \cdot min^{-1}$.

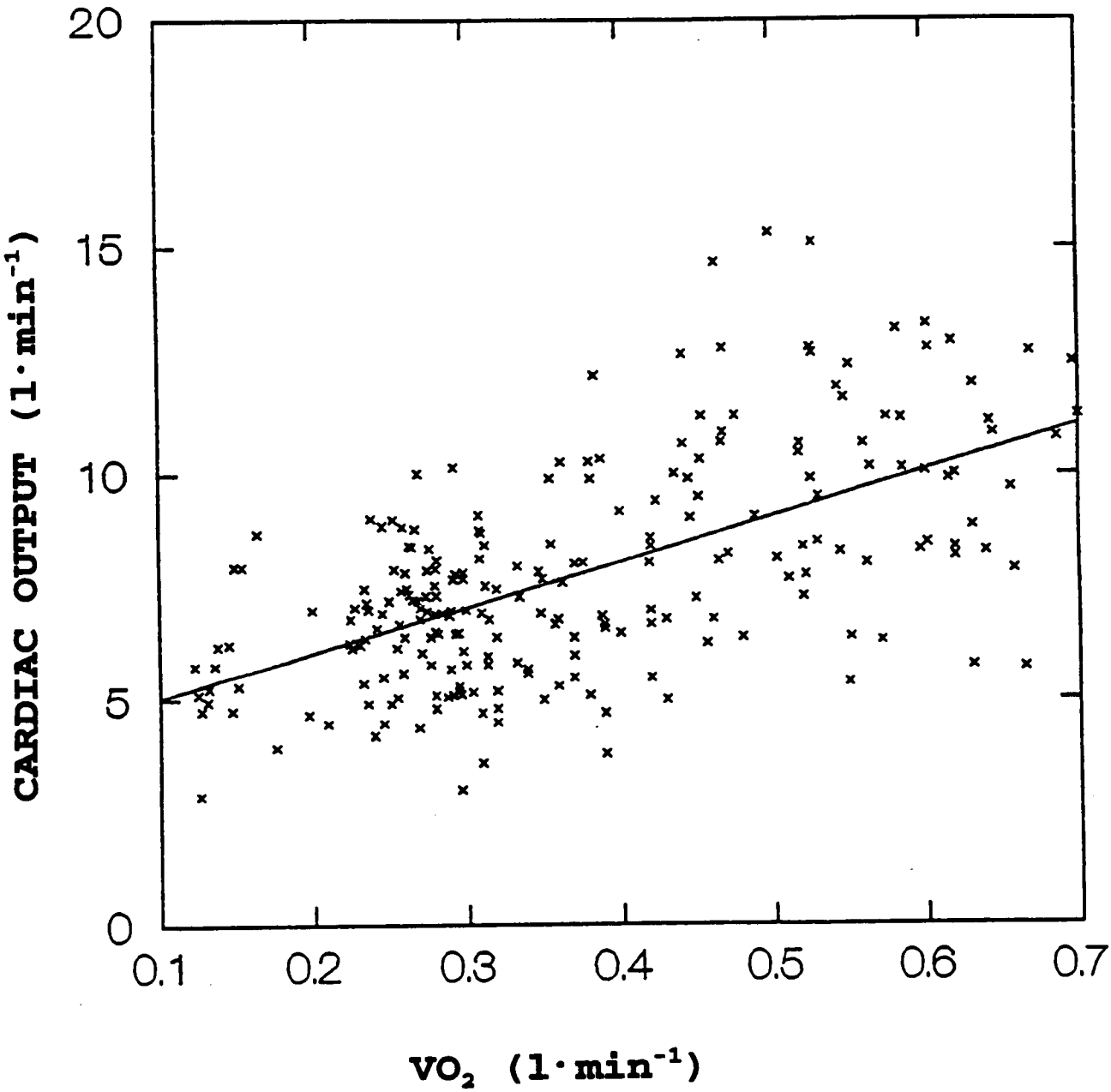


Figure 8. The regression line for cardiac output as a function of oxygen uptake is compared to individual female values with VO_2 values less than or equal to 0.7 $l \cdot min^{-1}$.

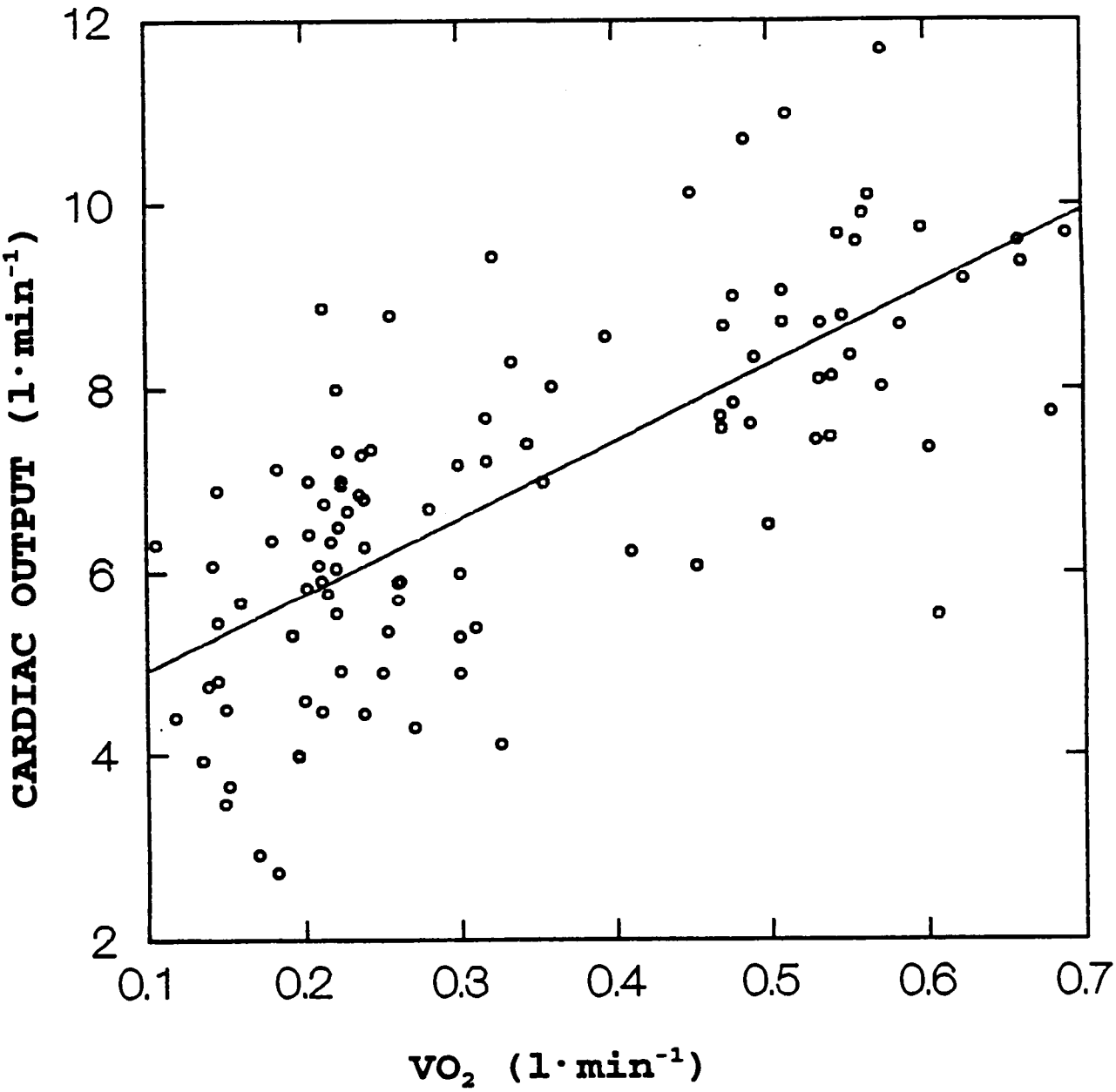


Figure 9. The regression line for cardiac output as a function of oxygen uptake is compared to individual values for males and females with VO_2 values greater than 0.7 $l \cdot min^{-1}$.

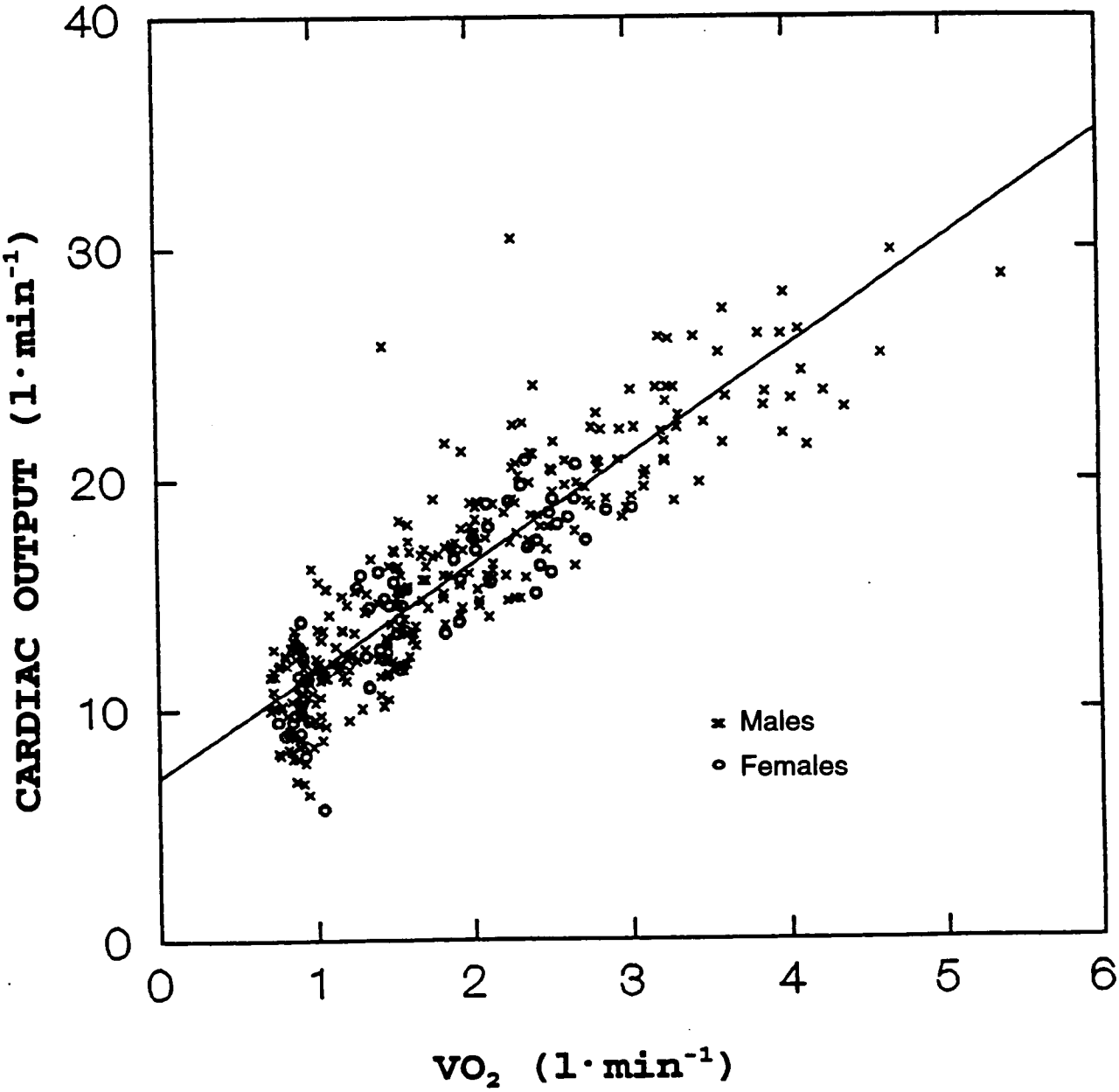


Figure 10. The regression line for cardiac index as a function of oxygen uptake is compared to individual values for males and females with VO_2 values less than or equal to 0.7 $l \cdot min^{-1}$.

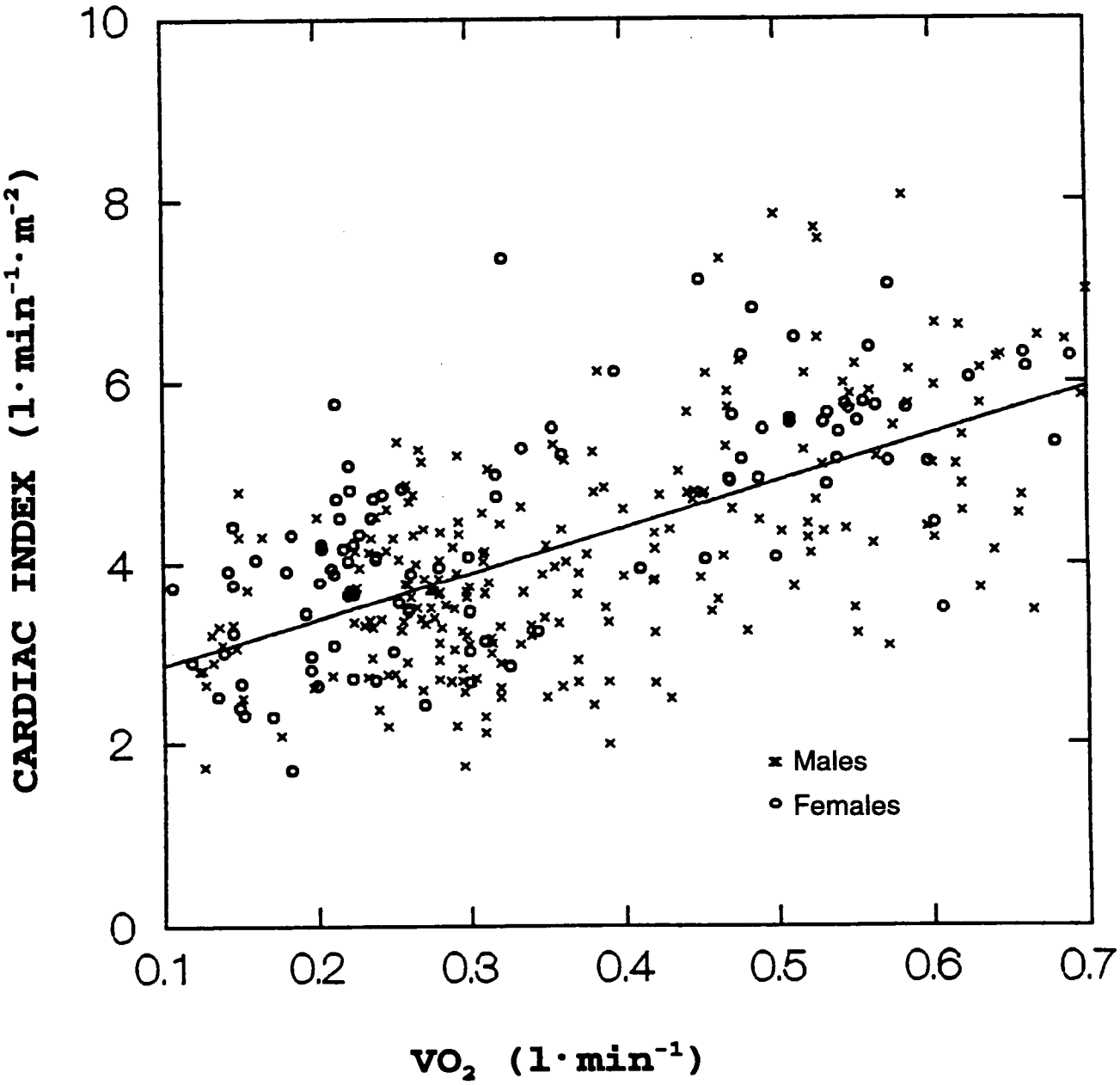
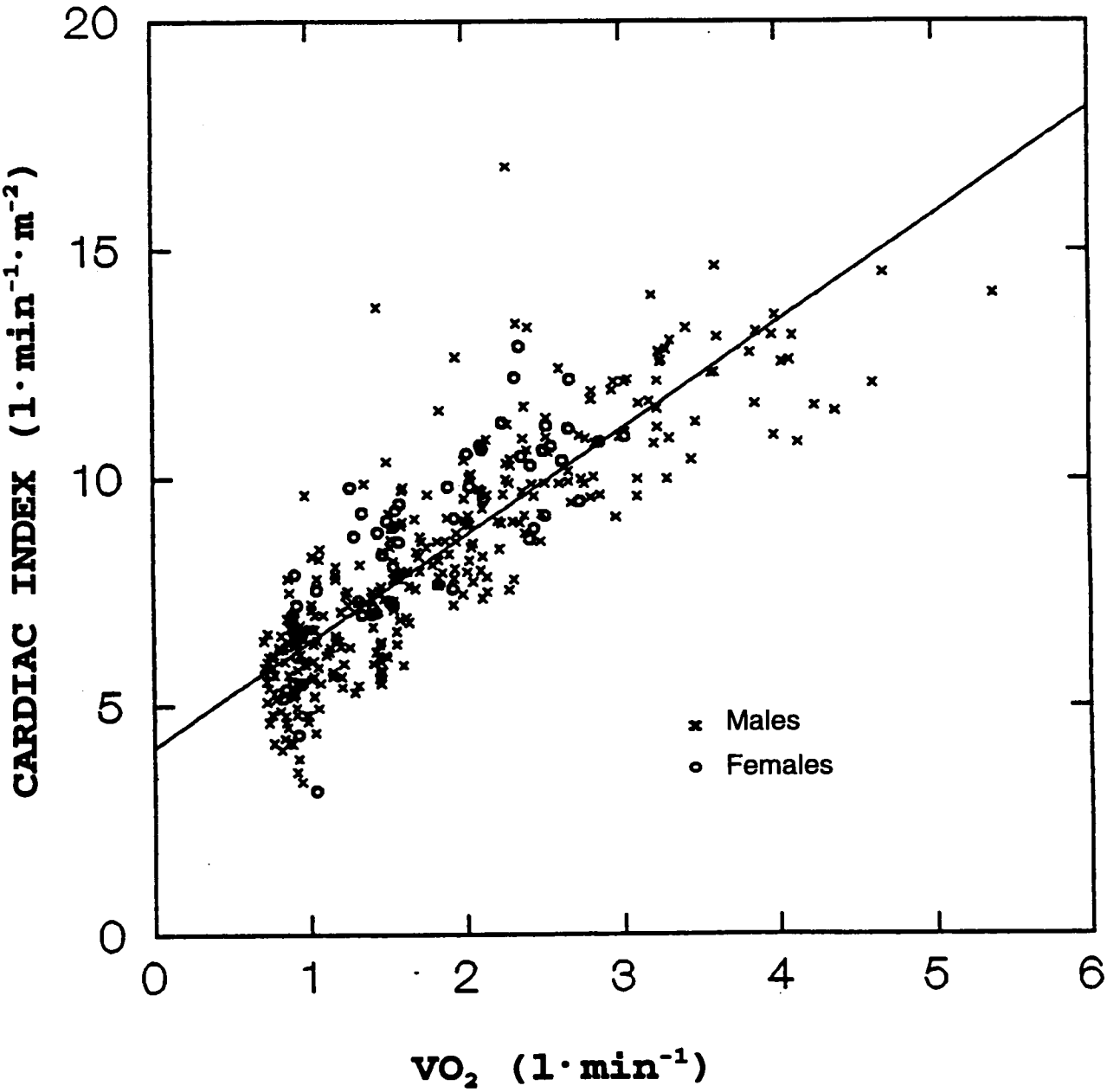


Figure 11. The regression line for cardiac index as a function of oxygen uptake is compared to individual values for males and females with VO_2 values greater than 0.7 $l \cdot min^{-1}$.



F. Cardiac output during pregnancy

Methods used to estimate CO before the introduction of the Cournand technique were inaccurate and tended to underestimate CO, but some qualitative information can be obtained from the earlier results. In a summary of earlier studies, Hamilton (1949) reported an increase in CO during the first two trimesters of pregnancy that amounted to 45-85% of the non-pregnant level. Cardiac output reached a maximum by the 32nd week of pregnancy and there was a significant decrease in CO during the last four weeks of pregnancy. In studies using the Cournand technique, researchers (Adams 1954, Bader et al. 1955, Hamilton 1949, Rovinsky and Jaffin 1966, Roy et al. 1966, Ueland et al. 1969, Walters et al. 1966) reported comparable changes in supine CO during pregnancy.

The variation in basal CO among individuals makes it difficult to draw meaningful conclusions about changes in CO during pregnancy from studies that do not include serial measurements of subjects. Some studies (Adams 1954, Roy et al. 1966, Walters et al. 1966) contained serial measurements, but other researchers measured the CO of any particular individual at only one point during the pregnancy.

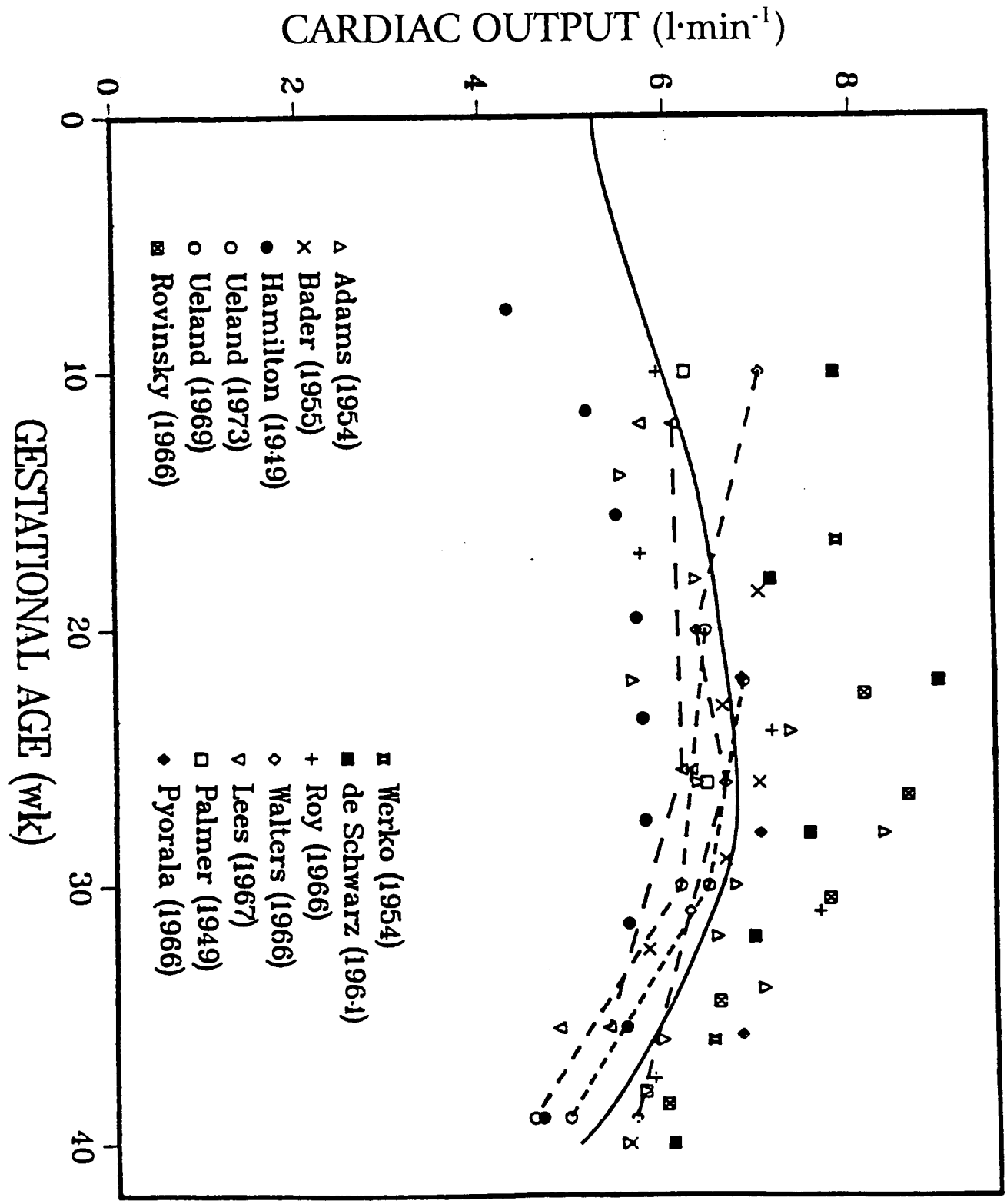
An additional problem occurs in studies that report supine CO but do not report CO in other body positions. It is now generally accepted that in the supine position there is a postural phenomenon that causes a significant decrease in CO during the last month of pregnancy due to a reduction in venous return following occlusion of the inferior vena cava by the uterus (Bieniarz et al. 1966). During the early stages of pregnancy, the decrease in CO in moving from supine to upright position is similar to the change observed in nonpregnant controls, but researchers (Lees et al. 1967, Pyorala 1966, Ueland et al. 1968, Ueland et al. 1973) report little difference in supine and upright CO during the latter stages of pregnancy. Also, with nonpregnant controls and during early stages of pregnancy there appears to be little difference between supine CO and lateral CO, but researchers have found that lateral CO is greater than supine CO during the latter stages of pregnancy (reported averages range from 12% to 34%) (Campbell et al. 1985, Lees et al. 1967, Ueland et al. 1968, Ueland and Hansen 1969). The magnitude of the decrease in supine CO during the last trimester of pregnancy is approximately the same as the decrease in CO caused by moving from a lateral measurement to a supine measurement.

Results of studies on CO during pregnancy are insufficient for very precise statements about the change during and after pregnancy, but some general conclusions can be drawn. Supine CO returns to normal nonpregnant levels within 2-3 w postpartum (Adams 1954, Hamilton 1949). The

increase in CO corresponding to a given increase in oxygen uptake during pregnancy is comparable to the nonpregnant response (Bader et al. 1955, Ueland et al. 1969). In any given body position, there appears to be a 15-25% increase in CO by the beginning of the second trimester, and by the 28th to 32nd gestational week the maximum increase of 20-40% over the nonpregnant CO is achieved. Upright and laterally measured CO values do not decrease during pregnancy, but supine CO decreases during the last month of pregnancy to approximately the same level as the nonpregnant supine CO. Although there is a slight increase in resting oxygen uptake as the pregnancy progresses, the increase in oxygen uptake is not enough to explain the increase in CO (Bader et al. 1955, Ueland et al. 1973).

A suggested reference curve for supine cardiac output during pregnancy is presented in Figure 12. Data from studies giving average CO values at various stages of pregnancy are also plotted for comparison. Data from longitudinal studies are connected by dotted lines. Suggested reference curves for upright or lateral cardiac output during pregnancy would have approximately the same shape during the first two trimesters of pregnancy, but they would not decrease during the last trimester of pregnancy.

Figure 12. The suggested reference curve (solid line) for supine cardiac output during pregnancy is compared to average values obtained from various studies. Values from studies containing serial measurements are connected by dotted lines.



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IV. SUMMARY

Total blood volume for newborn infants can be reasonably estimated using a multiple of body weight, and TBV for children can be estimated using linear functions of weight and age for each sex. Reasonable estimates of TBV for adults can be obtained using linear expressions involving weight and height or weight and a power of height. The standard deviation in male or female TBV at a fixed age is 20-25% of the TBV value for children and approximately 15% of the TBV value for adults.

There does not appear to be a single method of standardization of CO with respect to a measure of body size that would give comparable distributions of values over all age ranges. Standardization with respect to BSA does not appear to explain a significant amount of the variation in adult CO, but it does appear to remove the sex difference in the cardiac output distributions at a fixed age. For young and middle aged adult males and females, CO can be expressed as an increasing linear function of BSA and a decreasing linear function of age. The coefficient of variation (standard deviation divided by the mean) in CO or CI values is 0.25-0.30 for children and 0.20-0.25 for adults in each sex group.

Resting CO appears to be at its maximum when the subject is lying horizontally. The resting seated CO is 15-20% less and the resting standing CO is 20-25% less than the CO value that is measured with the subject lying horizontally.

There is a significant correlation between CO and oxygen uptake in any fixed body position as the subject changes from a resting state to a state of light exercise. The slope of the relationship is near 8 for females and near 10 for males; each unit increase in oxygen uptake roughly corresponds to an 8-10 unit increase in CO. The correlation between CO and oxygen uptake is even higher as the subject progresses from light exercise to moderately heavy exercise, but the slope of the relationship is much less. At higher work loads, each unit increase in oxygen uptake corresponds to approximately a 5 unit increase in CO.

Resting CO of pregnant females measured with the subject upright or lying laterally increases throughout pregnancy with a possible leveling off during the latter stages of pregnancy. The resting pregnant CO may be 20-40% greater than the resting nonpregnant CO measured under the same conditions. Because of a reduction in venous return following occlusion of the inferior vena cava by the uterus, supine CO decreases toward the end of the pregnancy to values that approximate the nonpregnant supine CO.

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