Changes in Cardiac Output with Age

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In the first of two papers, the details and results of a systematic, carefully standardized application of dye dilution technic to the measurement of cardiac output are reported. A substantially reduced output was a consistent finding in older subjects. Factors responsible for this are analyzed in this article, and further interpretations are made in the succeeding article. One result of the analysis of time-concentration curves of dye provides an interesting relationship to clinical estimates of circulation time.

NVESTIGATIONS of cardiac output in older, but presumably "normal," adults - were made by Starr and his coworkers,¹ by Lewis² and by Apéria³ 16 to 20 years ago, using the indirect gas methods then available. Although the insensitivity of these methods could mask a sizeable change, Starr and his associates noted that in the "period before 20 years the average cardiac index is higher than at any time later, after 50 it slowly declines. The number of cases was too small to demonstrate the significance of the difference." Their series included only nine cases over 50 years of age; the oldest was 76. Lewis, in a systematic agewise study, found a small decrease in cardiac index in 100 male subjects between 40 and 89 years of age. He considered that the observed changes represented neither statistically nor physiologically a significant decline and that they were predominantly the result of a decrease in oxygen consumption. A decrease of about the same order may be calculated from the data reported by Apéria,³ utilizing the acetylene technic of Grollman. These indirect Fick gas methods are now recognized as yielding values which are approximately 25 per cent too low, but even allowing for this, a sizeable decrease in cardiac output cannot be said to have been demonstrated by these studies, despite a consistent suggestion in this direction.

Age comparisons, using the Fick principle with right heart catheterization, were sought in the studies of Stead and his colleagues,⁴ Cournand and his co-workers⁵ and Nickerson and associates.⁶ In the series of Stead and associates,⁴ the oldest subject was 39 years. Cournand and co-workers⁵ included 17 normal male subjects, the oldest of whom was 58 years. Among these there was a definite decrease in cardiac output with age. Nickerson and associates⁶ studied seven patients over 50 years old, the oldest being 57, but found no significant age change. Other studies, where cardiac catheterization was used, do not contain the number or range of subjects to provide agewise data.

In a recent report, Smith and colleagues,⁷ using an indicator dilution technic, obtained a mean cardiac index of 2.67 in 10 subjects age 62 to 77 years, average 71 years. They considered this to be an unexpectedly low value in comparison to a mean of 3.5 liters per minute for 10 subjects 22 to 55, average 52 years of age.

Many attempts to estimate cardiac output have been made by approximation formulas or by empiric constructions based on blood pressure, pulse^{8, 9} or ballistocardiographic records.^{10, 11} These methods do not measure cardiac output, nor do they provide reliable estimates for the individual. With the availability of an indicator dilution method for the determination of cardiac output, we set about to investigate this problem.

Methods

Subjects. Determinations of cardiac output by an indicator dilution method were made in 67 males between the ages of 19 and 86 years of age, (average age 52.5 years). According to clinical criteria these subjects were free of suspected relevant disease and they form the basis for an analysis of agewise change. Satisfactory duplicate determinations of

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cardiac output were performed in 53 of these subjects. Seven additional subjects who were not considered "normal" were added to provide a series of 60 subjects on whom reproducibility of the procedure was tested. These seven are not included in the agewise analysis. All patients were chosen from the wards of the Baltimore City Hospitals, after having been in the hospital and afebrile for at least five days prior to the test procedure. They were ambulatory and none had had any surgical procedure within five days prior to the test. Some were convalescing from respiratory infections or awaiting discharge after convalescing from orthopedic conditions. Many had recovered from acute illnesses months or years ago and were living in the Infirmary division of the Baltimore City Hospitals. All subjects were interviewed by one of the investigators (M. B.). None presented histories compatible with cardiovascular disease or had symptoms clearly referable to the cardiovascular system such as angina, orthopnea, exertional dyspnea, palpitations, persistent or evident ankle edema. None had ever taken any cardiotonic drugs. On physical examination, subjects showing evidence of valvular disease or aortitis, cardiac enlargement, significant arrhythmia, congestive failure, hypertensive disease or a casual brachial blood pressure exceeding 175 systolic or 90 mm. Hg diastolic were excluded; diabetic, hyperthyroid, anemic or immobile patients were also excluded. For this purpose anemia was judged by an arterial hematocrit below 33 per cent (with one exception, a subject 80 years of age whose hematocrit was 28 per cent*).

Venous pressure measured in an antecubital vein, using a 15 gage needle, was less than 12 cm. above the level of the atrium in all cases. Decholin circulation time was performed in all subjects and an ether circulation time was performed in approximately half of the subjects. Subjects with decholin circulation times as high as 30 seconds were not eliminated on this basis alone. All subjects in this series had recent electrocardiograms which were within normal limits as judged by the criteria of Burch and Winsor¹³. A teleoroentgenogram of the chest was obtained on each subject, and cases showing any pulmonary or mediastinal lesions suspected of being acute or extensive were excluded. The long and broad diameters of the cardiac silhouette were measured and no subject was included in the series, if the product of these measurements exceeded by 15 per cent the value predicted on the basis of the individual's height and weight.¹⁴

Procedure. The patients were in the basal state preceeding the test. After novocaine infiltration, a 15 cm. long polyethylene catheter was placed in a right antecubital vein and a thin wall 18 gage needle was placed in the left brachial artery. Cardiac rate and intra-arterial pressure were recorded before each determination of cardiac output. Approximately 5 mg. of Evans blue dye was delivered into the circulation through the catheter from a calibrated syringe, and blood was sampled from the brachial artery by a collection device similar to that described by Newman and co-workers.¹⁵ In most subjects a second determination was made 10 minutes after the completion of the first.

The optical density of the dyed serum was read promptly in microcells on a Beckman Model DU spectrophotometer at 620 m μ . The characteristics of the dye curves were read from concentration-time plots made on semilogarithmic paper. Determinations were also excluded from this series if the subject obviously was not basal, for example, if he coughed, moved about, or complained during the procedure.

Calculations

We have attempted to use terms and symbols consistent with the recent literature.^{16, 17} The data and derived values in the tables are based upon an average of one to three separately determined values for each item.

Cardiac Output (C.O. =
$$\frac{60 \ q}{A}$$
 liters per minute)

where q is the quantity of indicator dye injected in milligrams and A is the area under the time concentration curve in the absence of recirculation in milligrams per second per liter, derived by extrapolation and calculated by summation.¹⁸ Curves where extrapolation was uncertain, such as those with less than four points on the section of decreasing concentration prior to recirculation, were eliminated.

Heart Rate in beats per minute was measured as the reciprocal of the average cycle length of 10 consecutive brachial arterial pressure pulses recorded just before each determination of cardiac output.

Dye appearance time (A.T.) is the time in seconds between the beginning of injection and the time (t_a) at which a detectable *increase in dye* concentration (0.1 mg. per liter) occurred in a sampling tube. Dye passage time (P.T.) is the time in seconds between t_a and the time (t_d) at which estimated relative dye concentration had declined to 0.1 mg. per liter eliminating the estimated effect of recirculation. Mean time of a lag exponential $\left[(T_{1e}) = A.T. + \frac{1}{K} \right]$ where A.T. is the appearance time and $\frac{1}{K}$ is the reciprocal slope of the extra-

^{*} Brannon and associates¹² have shown that the cardiac output does not change unless the hemoglobin falls to a level of about 7 Gm. The included 80 year old subject whose hematocrit was 0.28 had a cardiac output which was not significantly different from the mean for his age group.

polated log concentration-time curve in seconds. *True mean transit time* (T) in seconds is obtained by summing the products of each blood sample concentration and its time and then dividing by the summed concentrations under the curve, i.e. the expression which closely approximates the

$$\bar{T} = \frac{\sum_{t_a}^{t_a} tc\Delta t}{\sum_{t_a}^{t_a} c\Delta t}$$

theoretic formula.16

Central Volume (V) was calculated as the product of cardiac output (C.O.) and mean time (\bar{T}) .

The statistical analysis and symbols used generally follow standard procedure.¹⁹ The statistics of simple linear regressions have been used as a convenient means of displaying results. To develop consistent expressions for some interrelated items, we have obtained linear regressions of logarithmic values. There is, however, no implication that either a linear or exponential relationship exists, in any or all measures, and our probability estimates are not substantially altered by either type of fit.

The predicted value at 50 years of age (\hat{Y}_{50}) has been selected in preference to the mean value (\bar{Y}) , as a basis of representation for comparison of items showing age trends: $\hat{Y}_{50} = Y - b\Delta a$, or $\hat{Y}_{50} = \bar{Y}e^{-b\Delta a}$, where Δa equals mean age minus 50 years and b is the coefficient of regression. From the linear expression, the average rate of change may be conveniently expressed as per cent of the 50 year value; $\left(\frac{100 \ b}{\hat{Y}_{50}}\right)$ and the predicted value (\hat{Y}) at any age: $\hat{Y} = \hat{Y}_{50} + b\Delta a$, where a equals age minus 50 years. From the exponential expression, 100 \times the regression coefficient (b) represents the average per cent change per year, and the predicted value $(\hat{Y}) = \hat{Y}_{50} e^{ba}$. An estimate of the error of a single determination was calculated as $\sqrt{\frac{\Sigma(Y_1 - \overline{Y}_2)^2}{g_N}}$ from duplicate determinations made on the same subject.

Results

In the 60 subjects for whom there were successful duplicate determinations, the estimated error of a single observation was 345 ml. per minute or 6.4 per cent, the difference between these two determinations in the same individual without regard to sign averaged 400 ml. per minute, or 7.9 per cent of the mean of the pair.*



FIG. 1. The relation between cardiac output and age in 67 'basal' males without circulatory disorder. Each point represents the average of two measurements in 49 subjects, of three measurements in four subjects, and a single measurement in 14 subjects. The line indicates the simple linear regression for the data in all figures. Figs. 1, 2, 3 and 5, are plotted on comparable ordinate scales by making the ratio of scale unit to mean value similar in these figures.

It is of interest that the absolute deviation between determinations varied directly with the magnitude of the cardiac output (r = 0.40)while the per cent difference was more constant.

Although the mean value of the first determination exceeded that of the second by 136 ml. per minute ($\sigma_d = 501$)[†], this difference was not statistically significant. The first value exceeded the second in 34 cases but was less in 26 cases. There was also no evidence of an age trend in the difference.

Cardiac Output (C.O.)—The basal cardiac output for all subjects averaged 5.08 liters per

 $\dagger \sigma_{\rm d}$ = standard deviation of the distribution.

^{*} In initial studies on the validation of the dye technic in our laboratory, Dr. Harold Silver performed a preliminary series of replicate determinations upon 16 patients, using essentially the same

technic except for a manually operated collection rack instead of the rotating disc. The average difference between pairs was also 400 ml. or 7.4 per cent of the mean of the pairs, and all values in this group except two agreed within 19 per cent. The estimated error of a single determination was 437 ml. per minute or 7.4 per cent. Smith and associates⁷ included a study of reproducibility in a recent report. Thirty-one of 34 pairs repeated within 40 minutes agreed within 15 per cent. Duplicate determinations were also reported by Cugell²⁰ in four patients.



FIG. 2. Cardiac index versus age. Legend as in figure 1.

minute ($\sigma_d = 1.51$). Table 1 lists salient data for the decade means^{*} with their standard deviation of the means. Figure 1 shows a scatter plot of the individual means. A decline in cardiac output is evident after the third decade. The coefficient of correlation of log C.O. with age for all data was highly significant (r =-0.69) and the regression of cardiac output on age averaged 1.0 per cent per year. While the per cent standard deviation of the distribution[†] was 31.4, the per cent standard deviation about regression[§] was substantially less, 21.8.

The cardiac index for all subjects (table 1) averaged 2.94 liters per minute per square meter of body surface area, ($\sigma_d = 0.78$). Figure 2 shows a scatter plot, and table 1 shows the mean index by decades to decrease with age in a manner similar to the fall in cardiac output. The age regression averaged 0.79 per cent per year.

Table 1 shows a small agewise decrease in

the decade means of calculated surface area of this group of subjects. The decrease is small but is statistically significant with a regression of -0.22 per cent per year. The total variation of surface area in the material was small with a standard deviation of $\pm .17$ M.², but nevertheless cardiac output showed a correlation of 0.43 with surface area, indicating that this method can differentiate the large from the small individual.

The average stroke volume (table 1) was 74.2 ml. per beat, ($\sigma_d = 18.9$). With two exceptions, the means of stroke volumes for each decade tend to diminish progressively. The overall correlation of age and stroke volume was high with an average decrease of 0.70 per cent of the beat output per year. The correlation of age and stroke volume was less striking than was the correlation of age and cardiac output, due to an agewise decrease in heart rate in these subjects. Thus the age decline in cardiac output per minute is in part attributable to an observed reduction in body size (surface area) and in part to a reduction in heart rate. When the stroke index (stroke volume per unit of surface area) was computed, the mean value was 43. ml. per beat per square meter ($\sigma_d = 9.5$) and the residual diminution with age is still highly significant at 0.49 per cent per year. A scatter plot is shown in figure 3. The foregoing, and other significant correlations and statistical analyses are summarized in table 2.

The interrelationships of cardiac output and age in our series may also be expressed as if the factors contributed by surface area and heart rate were removed, by the coefficient of partial correlation for cardiac output and age which was -0.50.

Although less conventional, it is at least equally applicable, and even more convenient, to express this data on the basis of body weight instead of surface area. The coefficient of variability is not lessened, nor is the simple correlation coefficient with age improved and the coefficient of partial correlation is -.54.

Estimates of circulation velocity and central volume. The appearance time (A.T.) of dye in the limb opposite to the injection site may be considered as an objective test of "circulation time". This averaged 14.1 seconds, ($\sigma_d = 2.6$).

^{*} At the request of the editor, the individual data have been omitted from table 1. These data will be furnished by the authors on request as long as copies are available. They have also been deposited with the Photoduplication Service, Library of Congress, Washington 25, D. C. as Document No. 4675.

^{† 100 (}antilog $\sigma_{d\log c.o.} - 1.0$).

^{§ 100 [}antilog $\sigma_{d\log c.o.}$ ($\sqrt{1.0 - r^2}$) - 1.0]

Age	n	Surface, Area, M.²	Heart Rate/min.	Cardiac Output, Liters/min.			Cardiac Index, L./min/	Stroke Volume,	Stroke Index, ml/beat/	Appear- ance Time.	Mean Transit Time.	Passage Time,	
				I	п	Aver.	M. ²	ml./beat	M.2	seconds	seconds	seconds	
Мп. σ _{Mn.}	23.6	9	1.75 .04	$76.9 \\ 4.6$	6.65	6.04	6.49 .51	3.72 .28	$\begin{array}{c} 85.6\\ 6.1\end{array}$	$\begin{array}{c} 48.9\\ 3.1\end{array}$	12.0 .7	$19.0\\1.0$	$\begin{array}{c} 26.1 \\ 1.4 \end{array}$
Mn. σ _{Mn.}	34.1	10	1.86 .06	$71.7 \\ 3.4$	6.69	6.11	6.57 .56	3.54 .30	$91.8 \\ 7.1$	$\begin{array}{c} 49.4\\ 3.8\end{array}$	13.5 .7	$\begin{array}{c} 21.3 \\ 1.8 \end{array}$	$\begin{array}{c} 29.3 \\ 4.4 \end{array}$
Мп. σ _{Мп.}	43.3	11	1.81 .04	$\begin{array}{c} 69.1\\ 3.0\end{array}$	5.34	5.51	$5.34\\.32$	2.96 .17	78.3 4.7	$\begin{array}{c} 43.3\\ 2.5\end{array}$	13.7.6	$\begin{array}{c} 24.0 \\ 1.8 \end{array}$	$\begin{array}{c} 36.8\\ 4.2 \end{array}$
Mn. σ _{Mn.}	54.8	11	$\begin{array}{c}1.67\\.05\end{array}$	69.8 2.8	4.74	4.47	4.63 .21	$\begin{array}{c} 2.78\\.13\end{array}$	$\begin{array}{c} 67.2\\ 3.1\end{array}$	$\begin{array}{c} 40.3\\ 2.2 \end{array}$	$\frac{13.9}{.9}$	$\begin{array}{c} 23.4 \\ 1.0 \end{array}$	$\begin{array}{c} 33.9\\1.7\end{array}$
Mn. σ _{Mn.}	65.4	10	1.67 .06	$\begin{array}{c} 63.0\\ 3.2 \end{array}$	4.34	4.34	$4.29 \\ .28$	$\begin{array}{c} 2.58\\.15\end{array}$	$\begin{array}{c} 69.5 \\ 4.9 \end{array}$	$\begin{array}{c} 41.5\\ 2.4\end{array}$	15.0.7	$\begin{array}{c} 25.9 \\ 1.2 \end{array}$	40.1 3.6
Mn. σ _{Mn.}	73.3	9	1.61 $.05$	$\begin{array}{c} 65.8\\ 3.6\end{array}$	4.36	3.94	$4.05 \\ .25$	$\begin{array}{c} 2.54 \\ .18 \end{array}$	$\begin{array}{c} 63.0\\ 4.7\end{array}$	$39.3 \\ 3.2$	$\begin{array}{c} 14.9 \\ .9 \end{array}$	$\begin{array}{c} 24.4 \\ 1.3 \end{array}$	$\begin{array}{c} 35.2 \\ 1.6 \end{array}$
Mn. σ _{Mn.}	82.0	7	1.64 .07	67.0 7.5	3.86	3.91	3.87 .39	2.36 .23	$\begin{array}{c} 60.1 \\ 5.1 \end{array}$	$\begin{array}{c} 36.5\\ 3.3\end{array}$	16.6 .9	$\begin{array}{c} 28.7 \\ 2.5 \end{array}$	41.1 4.3
Mn. σ _d σ _{Mn.}	$52.5 \\ 19.1 \\ 2.3$	67	1.72 .17 .02	$ \begin{array}{c} 69.1 \\ 12.1 \\ 1.5 \end{array} $			5.08 1.51 .18	2.94 .78 .10	$74.2 \\ 18.9 \\ 2.3$	43.0 9.5 1.2	14.1 2.6 $.31$	$\begin{array}{c} 23.6\\ 5.2\\ .6\end{array}$	$34.5 \\ 19.9 \\ 1.3$

TABLE 1.—Summary of Results by Decades



FIG. 3. Stroke output per square meter of surface area versus age. Legend as in figure 1.



FIG. 4. Circulation appearance time versus age. The time of first detection in the brachial arterial blood of T-1824 after injection of 5 mg. into the opposite antecubital vein under "basal" conditions.



FIG. 5. Circulation time versus age. The mean transit time of T-1824 from antecubital vein to brachial arterial blood after a 5 mg. injection.

Appearance time revealed a small but statistically significant increase with age averaging 0.06 second per year (tables 1, 2, and fig. 4). The mean transit time (\overline{T}) averaged 23.7 seconds ($\sigma_d = 5.2$), and increased by an average of 0.14 second per year (tables 1, 2, and fig. 5).

There is a trend toward splaying out of the entire time-concentration curve, evidenced best by the increase in passage time with age averaging 0.23 second per year, and supported by the observation that the rate of increase in mean transit time (\overline{T}) is twice the rate of the increase in appearance time.

The product of transit time (T) and cardiac output (C.O.) which is an estimate of central volume (V) showed a slight tendency to decrease with age.

True mean dye transit time was also compared with the mean time of a lag exponential (\overline{T}_{le}) , a value proposed to estimate mean circulation time.¹⁶ This difference averaged 3.5 seconds, and was highly significant. The effect of this difference increases with age since the $\overline{T} - \overline{T}_{le}$ difference shows an age correlation of 0.48.

Decholin "circulation time" with a mean value of 17.2 seconds, ($\sigma_d = 4.6$) showed an increase approximately twice as great as did appearance time (A.T.), averaging 0.13 second per year. The age increase in Decholin time approximated that for transit time (\overline{T}). The correlation coefficient between these two meas-

	Average 50 Yr. Value*	Standard Deviation of Distri- bution Per Cent†	Age Correlation Coefficient	Age Regression				
Item				Average Per Year‡	Average Per Cent Per Year‡	Standard Error Per Cent Per Year	Probabil- ity of Chance Effect§	
Cardiac output (L./min.)	5.01	32.1	691		-1.01	.130	<.001	
Cardiac index (L./min./M. ²)	2.91	28.1	611		79	.127	<.001	
Stroke volume (ml./beat)	72.90	29.7	516		70	.145	<.001	
Stroke index (ml./beat/M. ²)	42.34	25.5	410		49	.134	<.001	
Surface area (M. ²)	1.72	10.3	419		22	.058	<.001	
Heart rate (beats/min.)	68.7	19.7	325		31	.110	<.01	
Appearance time (sec.)	13.9	18.5	+.463	.063	. 45 🗚	.015	<.001	
Mean transit time (sec.)	23.4	22.1	+.495	.136	. 58 🗶	.030	<.001	
Passage time (sec.)	33.9	31.5	+.404	. 230	.68 🗶	.0646	<.001	
Central volume (L)	1.96	25.2	294	0075	38 🕷	.0030	<.02	
Mean transit minus theoretical transit time								
(sec.)			+.484					
Mean transit minus decholin time $(sec.)$			+.041					

TABLE 2.-Statistical Summary of Age Relationships

* Based on regression equation.

 $\dagger 100 \text{ (antilog } \sigma_{d \log y} - 1.0 \text{)}.$

[‡] Slope of regression equation.

§ Based on t test of ratio of slope of regression equation to its standard error.

Coefficient of variation.

* Slope of linear regression equation expressed as per cent of average 50 year value.

Author	No. of Subjects	Age Range	Average	Decrease in Card with Age	Vethod	
Author	No. of Subjects	Age Kange	ml./min./ M.² yr.*	Probability of chance effect [†]	Per cent of 50 yr. va 1e	Method
Lewis ²	103	40-101	3.6	>.20	0.2	acetylene
Starr, et al. ¹	78	8-76	8.4	>.05	0.4	ethyl iodide
Apéria ³	111	30 - 70 +	7.3	<.001	0.4	acetylene
Cournand, et al. ⁵	17	21 - 58	26.2	>.02	0.9	direct Fick
Present series	67	19-86	24.4	<.001	0.8	dye dilution

TABLE 3.-Summary of Published Measurements of Cardiac Index in Relation to Age

* Slope of linear regression equation.

† Based upon t test of ratio of slope of regression equation to its standard error.

ures (transit time and Decholin time) was 0.395 and the difference between them did not change with age. Thus agewise trends in Decholin time and in the mean transit time for dye (\overline{T}) supplied substantially the same information.

DISCUSSION

Values for cardiac output as here measured show a moderate range among individuals $(\sigma_d = \pm 32 \text{ per cent})$. Some of this variability* is associated with differences in age, for a sizeable and significant decrease in cardiac output amounting to slightly over 1 per cent of the 50 year value per year, has been demonstrated with age for the subjects constituting this study. Part of the decrease in output is associated with a decrease in body size and part with a decrease in the frequency of the heart beat, but the remainder-about half-is due to reduction in the blood pumped per beat per unit of body size. Cardiac index, i.e., cardiac output per unit of body surface, has been widely used in comparing individuals of divergent size, and is generally useful. A constant of proportionality between output and surface area has not been theoretically or empirically demonstrated, so that other denominators such as body weight¹ justifiably have been used for these comparisons also. Data from this laboratory²¹ have shown that while the rate of basal oxygen uptake decreases with age if expressed per square meter of surface area, it does not decline if the data are expressed per liter of body water (represented by antipyrine space). A body water measurement, therefore, may be considered to

provide another, and possibly better, estimate of functioning mass than does surface area. Comparison (of two different series of subjects) suggests that the rate of fall in cardiac output is greater than the rate of decrease in antipyrine space. This indicates that the agewise decrease in cardiac output cannot be explained simply as a decrease in functioning body mass. This relationship will be discussed further in the light of additional measures of cardiac and circulatory performance²². In table 3, previously published studies, from which statistics in comparable terms have been recalculated, are compared with the current series.[†] Our findings stand in contrast to the results obtained by Starr and coworkers¹, by Lewis² and by Apéria³ who used indirect gas analysis technics. The present study is in excellent accord with the small series reported by Cournand and his colleagues⁵ who used the direct Fick technic and also satisfactorily explains the observations of Smith, and associates⁷ in their control series of 10 subjects between 62 and 77 years of age. The presence of three subjects in the age group below 40 years who had cardiac outputs over 9 liters per minute does not detract significantly from the results. In other series, particularly in reports on the direct Fick method, such values are frequently encountered in younger subjects. It is possible, but cannot be established, that the younger subjects were less basal or more apprehensive than the older subjects and conse-

^{*} About half of the variance, which accounts for one third of the standard deviation.

[†] Data obtained by Olbrich and Woodford-Williams on age changes in dye dilution output have not yet been published in full. (Third Congress, International Association of Gerontology, London, July 19-23, 1954, Symposia and Abstracts, p. 195.)

quently had higher cardiac output and heart rates. The absence of an age trend in the difference between the first and second cardiac output does not bear out this possibility.

The average decrease in cardiac output (C.O.) exceeds the average increase in transit time (\overline{T}) ; thus their product (V) shows a tendency to decrease. This lack of evidence for any increase in central volume in our material is, therefore, no encouragement to the criticism that more of our older subjects had undetected heart disease. In addition the relation between cardiac output and transit time assists in an interpretation of age changes in the kinetics of dye dilution, as follows:

Although the increase in appearance time is most easily and plausibly interpreted as due to a reduction in the velocity of the first dye injected, and/or the fastest moving dyed blood, other factors must be considered. A longer appearance time will also result from (a) a longer traversal pathway, or (b) a slower rise in dye concentration up to the detectable level, without change in the velocity of the earliest arriving dyed blood.

The age increase in transit time was more striking than the increase in appearance time. The increase in transit time would also indicate a decreased mean velocity unless the equivalent traversal path was (a) longer or (c) cross sectional area was greater.

The increase in dye passage time (P.T.) with age, and the increasing spread between appearance time and transit time characterize a greater time dispersion of dyed blood at the sampling site. Since sampling is approximately proportional to blood flow, this reflects a greater final time dispersion in the artery. Such increased splay would be anticipated as a consequence of a decreased velocity, but also would result from (a) an increased length of path (c) a greater cross section, (d) a greater dispersion of individual transit times among multiple paths or (e) a greater mixing in a single path, i.e. more turbulence. It might also be noted that a greater initial dispersion could arise if (f) injection were slower or were made into (g) a venous segment of larger volume or (h) a vessel carrying a greater flow of blood.

The evidence that central volume (V) does

not increase indicates that a consideration of (a) and (c), i.e. length and cross sectional area are not paramount. Since only these, besides decreased velocity, are common to an explanation of increases in appearance time (A.T.), transit time (\overline{T}), their difference (\overline{T} -A.T.) and dye passage time (P.T.), a decrease in mean velocity clearly is implied by the increase in transit time with age.

The prolongation in mean transit time with age averaged 0.6 per cent of the 50 year value per year. Lacking estimates of length and cross-sectional areas, a factor of proportionality cannot be applied to yield linear velocity estimates for individuals or groups. The average prolongation in mean transit time is less than the 1.0 per cent per year average reduction in cardiac output. These values are not independent, since passage time which is related to mean transit time, forms the base of the area from which output is calculated, and the correlation between mean time and cardiac output was -.495. Thus the velocity change is consistent with the reduction in blood flow.

Transit time (\overline{T}) was observed to differ from the mean time of a lag exponential (T_{le}) , a proposed estimate of mean time^{15, 16} derived from a log slope of the descending limb of dye concentration plus appearance time. A difference between these values $(\overline{T} - \overline{T}_{le})$ becomes a measure of the divergence of the observed time concentration curve from a delayed exponential. Because the construction of the descending limb of the time-concentration curve converts it into an exponential decline, it is obvious that the difference between theory and results represents the contribution of the initial, rising part of the curve, which is not instantaneous. In comparisons of the type we have made, the initial portion of the time concentration curve therefore should not be neglected or assumed to be constant.

The correspondence between the age regressions of Decholin and dye times is reassuring to the clinical interpretation of subjective "circulation times." Our study was not designed to test this point, and, therefore, the circulation time procedure was not highly standardized. The data do not imply that subjective response to Decholin is determined by mean Decholin transit time at the receptor tissue, but merely indicate a similar regression to that for the dye mean transit time. The similarity between the results of subjective and objective technics fails to provide evidence that increased delay in effector response and/or recognition is a significant factor in the prolongation of Decholin time in our material.

Conclusions

Cardiac output was determined by an indicator dilution technique in 67 male subjects aged 19 to 86 years selected as being free of relevant disease. The variability of the procedure has been examined, and the estimated error of a single determination was found to be less than 7 per cent.

The cardiac output averaged approximately 5 liters per minute, with individual variation indicated by a 30 per cent standard deviation. Part of this scatter is attributable to age differences. The relationship between cardiac output and age is significant, revealing a reduction of about 1 per cent per year. The reduction in cardiac output in this material is the result of an agewise decrease in stroke index augmented by decreases in body size and heart rate.

Time-concentration curves of indicator were critically analyzed. Corresponding points on these curves tend to occur later in older subjects, while estimated central volume does not increase. This is interpreted as due to a diminution of the velocity of blood flow at least consistent with the observed reduction in volume flow.

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SUMMARIO IN INTERLINGUA

In 67 masculos—seligite como libere de relevante morbos—le rendimento cardiac esseva determinate per un technica a dilution de indicator. Le variabilitate del procedimento usate esseva investigate con le constatation que le estimate error de un determination unic es infra 7 pro cento. Le rendimento cardiac median esseva circa 5 litros pro minuta con variationes individual indicate per un deviation standard de 30 pro cento. Un parte de iste dispersion es attribuibile a differentias de etate. Le relation inter rendimento cardiac e etate es significative. Illo revela un reduction de circa un pro cento per anno. In le casos studiate per nos le reduction del rendimento cardiac es le resultato de un abassamento del indice del pulso in le curso del avantiamento de etate, augmentate per le reduction del dimensiones corporee e del velocitate del corde.

Esseva executate un analyse critic del curvas del concentration del indicator como function del tempore. Punctos correspondente in iste curvas tende a occurrer plus tarde in le caso de individuos a etates plus avantiate, sed le volumine central non se augmenta. Isto es interpretate como un effecto del diminution del velocitate del fluxo sanguinee a un grado al minus correspondente al observate reduction del fluxo de volumine.

REFERENCES

- ¹ STARR, I., DONAL, J. S., MARGOLIES, A., SHAW, R., COLLINS, L. H. AND GAMBLE, C. J.: Studies of the heart and circulation in disease; estimations of basal cardiac output, metabolism, heart size and blood pressure in 235 subjects. J. Clin. Invest. **13**: 561, 1934.
- ² LEWIS, W. H., JR.: Changes with age in the cardiac output in adult men. Am. J. Physiol. **121**: 517, 1938.
- ³ APÉRIA, A.: Contribution à l'étude de la physiologie de la circulation en relation avec l'age. Acta med. scandinav. suppl. 89: 214, 1938.
- ⁴ STEAD, E. A., JR., WARREN, J. V. MERRILL, A. J. AND BRANNON, E. S.: The cardiac output in male subjects as measured by the technique of right atrial catheterization; normal values with observations on the effect of anxiety and tilting. J. Clin. Invest. **24**: 326, 1945.
- ⁵ COURNAND, A., RILEY, R. L., BREED, E. S., BALDWIN, E. DE F. AND RICHARDS, D. W.; Measurement of cardiac output in man using the technique of catheterization of the right auricle or ventricle. J. Clin. Invest. 24: 106, 1944.
- ⁶ NICKERSON, J. L., WARREN, J. V. AND BRANNON, E. S.: The cardiac output in man; studies with the low frequency, critically-damped ballistocardiograph and the method of right atrial catheterization. J. Clin. Invest. **26**: 1, 1947.

- ⁷ SMITH, W. W., WIKLER, S. AND FOX, A. C.: Hemodynamic studies of patients with myocardial infarction. Circulation 9: 352, 1954.
- ⁸ WEZLER, K. AND BÖGER, A.: Wachstum und Altern im Kreislauf. Klin. Wchnschr. 215: 257, 1936.
- ⁹ APÉRIA, A.: The physical calculation of the cardiac output and its error sources. Acta physiol. scandinav. 3: 237, 1941-42.
- ¹⁰ STARR, I. AND SCHROEDER, H. A.: Ballistocardiogram II normal standards, abnormalities commonly found in diseases of the heart and circulation and their significance. J. Clin. Invest. 19: 437, 1940.
- ¹¹ TANNER, J. M.: The construction of normal standards for cardiac output in man. J. Clin. Invest. 28: 567, 1949.
- ¹² BRANNON, E. S., MERRILL, A. J., WARREN, J. V. AND STEAD, E. A., JR.: The cardiac output in patients with chronic anemia as measured by the technique of right atrial catheterization. J. Clin. Invest. 24: 332, 1945.
- ¹³ BURCH, G. E. AND WINSOR, T.: A Primer of Electrocardiography. Ed. 2, Philadelphia, Lea and Febiger, 1953.
- ¹⁴ UNGERLEIDER, H. E. AND CLARK, C. P.: A study of the transverse diameter of the heart silhouette with prediction table based on the teleoroentgenogram. Tr. A. Life Insur. M. Dir. America 25: 84, 1938.
- ¹⁵ NEWMAN, E. V., MERRELL, M., GENECIN, A., MONGE, C., MILNOR, W. R. AND MCKEEVER,

W. R.: The dye dilution method for describing the central circulation; an analysis of factors shaping the time-concentration curves. Circulation 4: 735, 1951.

- ¹⁶ MEIER, P. AND ZIERLER, K. L.: On the theory of the indicator-dilution method of measurement of blood flow and volume. J. Appl. Physiol. 6: 731, 1954.
- ¹⁷ WOOD, E. H. AND SWAN, H. J. C.: Definition of terms and symbols for description of circulatory indicator-dilution curves. J. Appl. Physiol. 6: 797, 1954.
- ¹⁸ HAMILTON, W. F., RILEY, R. L., ATTYAH, A. M., COURNAND, A., FOWELL, D. M., HIMMELSTEIN, A., NOBLE, R. P., REMINGTON, J. W., RICH-ARDS, D. W., WHEELER, N. C. AND WHIT-HAM, A. C.: Comparison of Fick and dye injection methods of measuring cardiac output in man. Am. J. Physiol. 153: 309, 1948.
- ¹⁹ Peters, C. C. and Van Voorhis, W. R.: Statistical Procedures and Their Mathematical Bases. New York, McGraw-Hill, 1940, p. 516. ²⁰ CUGELL, D. W.: Cardiac output in epidemic
- hemorrhagic fever. Am. J. Med. 16: 668, 1954.
- ²¹ Shock, N. W., Yiengst, M. J. and Watkin, D. M.: Age change in body water and its relationship to basal oxygen consumption in males. J. Gerontol., 8: 388, July 1953. (Abstract).
- ²² LANDOWNE, M., BRANDFONBRENER, M. AND SHOCK, N. W.: The relation of age to certain measures of performance of the heart and the circulation. Circulation 11: 567, 1955.