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Circulation. 1978;57:1185-1190
doi: 10.1161/01.CIR.57.6.1185
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

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Pulmonary Hemodynamics and Right Ventricular Function in Hypertension

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SUMMARY **Pulmonary and systemic hemodynamics in 16 hypertensive subjects (group I) with left ventricular (LV) hypertrophy (ECG and echo criteria) and in 17 hypertensive subjects with ECG signs of LV strain (group II), were compared with those in 14 normal individuals. An augmented pulmonary arteriolar resistance (PAR) in group I and to a larger extent in group II accounted for the pulmonary pressure elevation in both groups. Increase in PAR was unrelated to pulmonary blood flow and volume, pleural pressure, arterial PO_2, PCO_2 and pH, and could not be explained entirely by the left ventricular end-diastolic pressure changes.**

In group I, left (L.MSEJR) and right (R.MSEJR) mean systolic ejection rate, stroke index (SI) and mean velocity of circumferential fiber shortening (V_{CF}) were enhanced in spite of the heightened pressure load on both sides of the heart. In group II, a large reduction of SI, L.MSEJR, R.MSEJR and V_{CF}, as well as the relationship between ventricular filling pressures and SI, documented a compromised performance of both ventricles.

Findings indicate that: systemic hypertension is associated with elevation of pulmonary arterial pressure and of PAR which is not necessarily a consequence of impairment in LV function; LV hypertrophy is associated with enhanced performance of either ventricle; in coincidence with development of ECG signs of LV strain, the performance of both sides of the heart deteriorates.

A functional interdependence of the two ventricles is suggested.

AVAILABLE INFORMATION on the dynamics of the right side of the heart and lesser circulation in systemic hypertension is scanty and somewhat discordant. Normal values of pulmonary pressure in subjects with systemic hypertension have been recorded in some studies.[1, 2] Elevated values were detected in hypertensive patients with left ventricular failure and were interpreted as a backward effect of this dysfunction.[3] Werkö and Lagerlöf,[4] however, reported that in a considerable number of cases of arterial hypertension without clinical signs of heart failure, pressure in the pulmonary artery is somewhat higher than the highest recorded in cases with normal circulation.

Cohn and coworkers have pointed out that if one calculates right ventricular functional characteristics in hypertension, impairment in the performance of the right ventricle can be demonstrated because the filling pressure is augmented and the right ventricular stroke output is diminished or changed little from normal.[5] If the concept is

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Received August 29, 1977; revision accepted January 10, 1978.

accepted that in hypertensive subjects variations in the pulmonary artery and in the right side of the heart occur secondarily to left ventricular failure, the mechanism of the right ventricular dysfunction is not clear. The classical theory that chronic elevation of pulmonary artery pressure secondary to left ventricular failure causes failure of the right ventricle,[6] is not totally satisfactory because it does not seem entirely reasonable that the right ventricle would fail after relatively short-term exposure to only modest elevation of pulmonary arterial pressure.

The present investigation was undertaken for the purpose of examining the relationship between left ventricular load and function; left ventricular function and pulmonary hemodynamics; pulmonary arterial pressure and right ventricular function; function of the right and the left side of the heart.

Materials and Methods

Thirty-three men in hospital with primary arterial hypertension were the subjects of the present report. All had repeated auscultatory readings of blood pressure above 180/100 mm Hg. Diagnosis of uncomplicated essential hypertension was made on the basis of the ordinary clinical tests. Criteria for selection of patients were: absence of history or signs referable to heart failure, pulmonary disease, valvular lesions, substernal pain, old myocardial infarction, idiopathic myocardial disease in addition to hypertension; glomerular filtration rate above 60 ml/min, normal serum concentration of potassium, sodium and chloride; regular sinus rhythm without conduction abnormalities; no digitalis at any time in the past or antihypertensive therapy for at least one month before entry; ability to record a technically satisfactory left ventricular echocardiogram.

The electrocardiogram, taken at rest at standard sensitivity and speed, presented in all these subjects either voltage changes of left ventricular hypertrophy (sum of the tallest and deepest precordial R and S waves exceeding 4.5 mV),[7] with normal ST segment and T wave, or ST depression and T wave inversion in addition to the voltage increase.

Healthy volunteers or patients in the hospital without signs of circulatory disorders and without medications which could interfere with their cardiovascular function, were also investigated as controls (14 cases). All subjects involved in the study gave free consent to the investigation with full knowledge of the procedures to be undertaken.

One week after the admission, during which the diagnosis of essential hypertension was made, and after the patients had been familiarized with the laboratory as well as with the investigators, circulatory measurements were performed in the fasting state, in the supine position, without premedication. A number 7 flow-directed Swan-Ganz catheter was inserted percutaneously, under local anesthesia, into an antecubital vein and floated, under fluoroscopy, to the pulmonary artery or advanced to the wedge position. A number 6 polyethylene radiopaque catheter, introduced percutaneously into a brachial artery and advanced to the root of the aorta, was used to monitor arterial pressure and to sample blood for cardiac output. Reproducible dye dilution curves were obtained by a Gilford densitometer after rapid injection of indocyanine green dye (5 mg) into the main pulmonary artery just beyond the pulmonary valve. The area under each dye dilution curve was measured by a planimeter; cardiac output and pulmonary blood volume were calculated by the standard Hamilton method.[8] The mean transit time was corrected for the delay, which was determined directly in each case, introduced by the sampling system, including catheter and densitometer cuvette. Pressures were determined with Statham P23De and P23Db strain gauge transducers, which were balanced against atmospheric pressure. The zero reference level for pressure recordings was 5 cm below the sternal angle. Mean pressures were obtained by electronic damping. The criteria for a satisfactory pulmonary artery wedge pressure were: change from the typical pulmonary artery pressure waveform to the typical pulmonary artery wedge pressure waveform upon inflation of the balloon catheter, and a mean pressure step-up upon deflation of the balloon catheter. The pulmonary artery wedge pressure was characterized by distinct "a" and "v" waveforms, with the "v" wave occurring after the T wave of the electrocardiogram. Left ventricular end-diastolic pressure was estimated by the "a" wave of the wedge pressure tracing. Measurements of right and left ventricular ejection times were obtained, respectively, by recordings (on an 8-channel Hewlett-Packard ink recorder, model 7868/A) at a paper speed of 100 mm/sec, of pulmonary and aortic pressure tracings (from the beginning upstroke to the trough of the incisura), according to the methods indicated by Leighton et al.[9] Both intervals were calculated from the mean of measurements on five consecutive beats, each read to the nearest 5 msec. The right (R.MSEJR) and left (L.MSEJR) mean rates of systolic ejection (index) were determined by dividing the stroke index by the right and left ventricular ejection times, respectively. Systemic vascular resistance (SVR) and pulmonary arteriolar resistance (PAR), in dynes · sec · cm^{-5}, were calculated from the following formulas:

$$SVR = \frac{\overline{AP} - \overline{RAP} \times 1332 \times 60}{CO\ (ml/min)},$$

$$PAR = \frac{\overline{PP} - \overline{PWP} \times 1332 \times 60}{CO\ (ml/min)},$$

where $\overline{AP}$ is mean systemic arterial pressure, $\overline{PP}$ is mean pulmonary arterial pressure, $\overline{RAP}$ is mean right atrial pressure, $\overline{PWP}$ is mean pulmonary arterial wedge pressure, and CO is cardiac output.

In each subject pleural pressure was estimated according to the method indicated by Milic-Emili et al.[10] In brief, a rubber 2 ml volume esophageal balloon was introduced through the nose into the esophagus, placed at a distance of 45 cm from the balloon tip to the nares, and connected to a pressure transducer through a polyethylene tube. Pleural pressure and circulatory variables were recorded simultaneously on the same recording system during quiet regular respiration.

Echocardiography was performed in all of the subjects with an ECHO-Cardio-VISOR, Organon Teknika, ultrasound unit. The left ventricular minor axis was measured by the technique described by Feigenbaum et al.[11] Patients were recumbent in a slight lateral decubitus position with 20° elevation of the head; the transducer was placed in the third or fourth left sternal interspace, and was directed posteriorly

and medially until the characteristic pattern of mitral valve motion was observed. The ultrasonic beam was then directed laterally and slightly inferiorly to locate a plane in which the motion of the interventricular septum and the left ventricular posterior wall components (endocardium and epicardium) could be detected simultaneously. The gain, damping and reject controls were adjusted to resolve echoes optimally from these structures with their characteristic patterns of motion. These movements were displayed in a time-motion mode and recorded by a Honeywell strip chart recorder. The tip of the mitral valve was chosen as an anatomic landmark which provided the best reproducible reference point along the left ventricular long axis for comparing quantitative measurements in different hearts. The left ventricular internal dimensions were measured at end diastole simultaneously with the R wave of the electrocardiogram, and at end systole at a time when posterior wall and septum maximally approached each other; the distance was taken from the endocardial echo of the posterior wall to the echo of the left side of the septum. The thickness of left ventricular posterior and interventricular septal walls was estimated by measuring the distance between the posterior wall endocardial and epicardial echoes, and, respectively, between the right and left endocardial echoes of the septum, at end diastole. From these measurements left ventricular circumferential wall stress (CWS), and mean velocity of circumferential shortening (V_{CF}) were calculated. CWS at the time of aortic valve opening was taken as an index of left ventricular afterload, and estimated by the formula of Sandler and Dodge[12] modified by Ratshin et al.[13]:

$$CWS = \frac{P\,D/2}{h}\left[1 - \frac{D}{8\,(D + h)}\right],$$

where P is the aortic end-diastolic pressure (dynes • cm^2), D is the ultrasonically measured ventricular internal minor dimension (cm), h is the ultrasonically measured ventricular wall thickness (cm). The normalized mean velocity of circ-circumferential shortening (circ/sec) was derived from the equation of Fortuin et al.[14]:

$$V_{CF} = \frac{S_D - S_S}{LVET \times S_D},$$

where S_D is the end-diastolic diameter, S_S is the end-systolic diameter, and LVET is the left ventricular ejection time.

All the hemodynamic and echocardiographic measurements were carried out in the steady state, which was considered to be achieved when patients felt comfortable, when heart rate and pressures had definitely stabilized; in each case, however, measurements were commenced at least 30 min after completing the endovascular procedures. The series of determinations were performed twice, at 15 min intervals; the average of the two measurements was taken as the representative value of each subject.

Determinations of PO_2, PCO_2 and pH were performed on an arterial blood sample withdrawn during quiet regular respiration. The pH was determined using the apparatus described by Siggaard-Andersen et al.[15] When this had been completed, portions of the sample were equilibrated with 4% CO_2 in O_2, and with 8% CO_2 in O_2, according to the standard Astrup procedure. The PCO_2 was obtained using the nomogram described by Siggaard-Andersen.[15] At the time of equilibration oxygen tension was determined with a Radiometer PO_2 electrode, type E 5046. The final values for each subject were the averages of measurements in triplicate.

Statistical significance of the differences between normal and hypertensive subjects, and between the two hypertensive groups was evaluated through the analysis of variance, on an Olivetti desk top computer, Model 101.

Results

In a previous study it was documented that ST-segment depression and T wave inversion in hypertension usually reflect a high level of hemodynamic load on the left ventricle.[16] It was felt that separation of the hypertensive patients into two groups, according to the presence (group II, 17 cases) or the absence (group I, 16 cases) of alterations in the repolarization phase of the electrocardiogram, could facilitate the analysis of the relationship between cardiac load and function, as well as between the function of the two ventricles.

Age and body surface area were comparable in hypertensives, and not significantly different from controls. The three groups were also quite homogeneous as regards pulmonary blood volume, pleural pressure, respiratory gases and pH of the blood (table 1). The echocardiographic measurements are reported in table 2. Interventricular septum and left ventricular posterior wall thicknesses were similar in group I and II, and significantly exceeded those of normal subjects. In group II end-diastolic and end-systolic minor axes were significantly greater than in the control and hypertensive group I subjects. In the latter these dimensions tended to be somewhat less than normal; the differences, however, were statistically not significant.

The averages of the examined hemodynamic functions are presented graphically in figure 1. Systemic systolic (SAP) and diastolic (DAP) arterial pressures were less elevated in group I than in group II; since cardiac index (CI) was normal in the former and reduced in the latter, systemic vascular resistance (SVR) was augmented in either group,

TABLE 1. *Arterial pH, PO_2, PCO_2, Pleural Pressure and Pulmonary Blood Volume*

Groups	pH	PO_2 (mm Hg)	PCO_2 (mm Hg)	Pleural pressure (mm Hg) Insp.	Exp.	Pulmonary blood volume (ml)
Control subjects	7.433	91.7 (2.6)*	35.07 (2.6)	−5.7 (.94)	−2.03 (.7)	1161 (221)
Hypertensive group I	7.435	92 (2.5)	34.37 (2.7)	−5.61 (.99)	−1.93 (.78)	1242 (336)
Hypertensive group II	7.433	91.2 (3)	35.43 (1.96)	−5.67 (.91)	−2.1 (.79)	1179 (390)

*Averages and SD.
The differences between hypertensive groups and control subjects are not significant.

TABLE 2. *Echocardiographic Values*

Groups	LV posterior wall thickness (cm)	LV septal wall thickness (cm)	LV internal dimensions (cm) S_D	LV internal dimensions (cm) S_S
Control subjects	1 (.12)‡	1.05 (.14)	4.85 (.20)	3.42 (.19)
Hypertensive group I	1.22 (.17)*	1.28 (.20)*	4.65 (.38)	3.23 (.27)
Hypertensive group II	1.25 (.14)*	1.33 (.22)*	5.42 (.22)*†	4.33 (.41)*†

*Differences from the control group significant at $P < 0.01$.
†Differences between the hypertensive groups significant at $P < 0.01$.
‡Averages and SD.

with a greater value in group II. The averages of systolic (SPP), diastolic (DPP) and mean wedge ($\overline{PWP}$) pulmonary pressures were quite similar in the two hypertensive groups and significantly higher than normal; pulmonary arteriolar resistance (PAR) was elevated in group I and to a larger degree in group II. Left ventricular mean velocity of circumferential fiber shortening (V_{CF}) was enhanced in group I and reduced in group II, and was paralleled by a similar pattern of the mean systolic ejection rate (L.MSEJR). The increment of the latter parameter in group I and its diminution in group II were related to a stroke index somewhat larger and a time of ejection shorter than normal, and, respectively, to a reduced stroke index and a lengthened ejection period. V_{CF} and L.MSEJR were increased in group I in spite of an augmented circumferential wall stress (CWS). In either group the functional pattern of the right

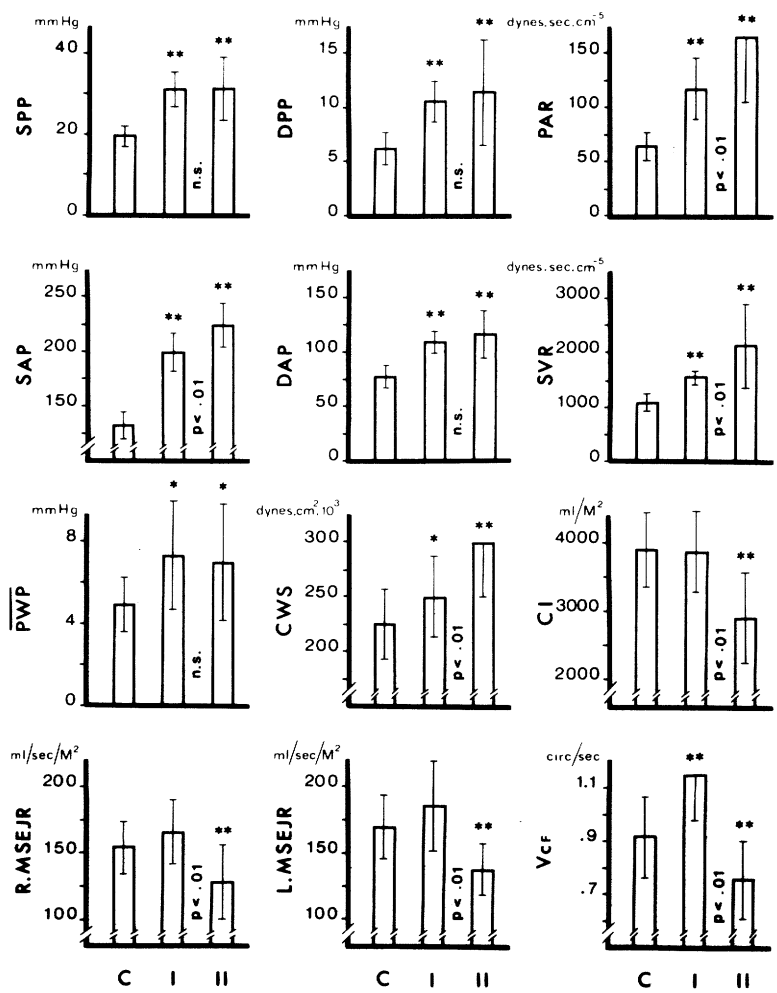

FIGURE 1. *Hemodynamic functions in 14 normotensive control subjects (C) and in two groups of essential hypertensive patients: group I, 16 patients with ECG voltage changes of left ventricular hypertrophy; group II, 17 patients with ST depression and T wave inversion in addition to voltage increase. Bars represent the mean for the group (SD). * and ** indicate* P *values of* < 0.05 *and* < 0.01, *respectively, for differences between the hypertensive groups and the control subjects.* P *values for differences between the hypertensive groups are indicated in the figure. SPP, systolic pulmonary pressure; DPP, diastolic pulmonary pressure; PAR, pulmonary arteriolar resistance; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; SVR, systemic vascular resistance;* $\overline{PWP}$, *mean pulmonary wedge pressure; CWS, left ventricular circumferential wall stress; CI, cardiac index; R.MSEJR and L.MSEJR, right and left mean systolic ejection rate;* V_{CF}, *left ventricular mean velocity of circumferential fiber shortening.*

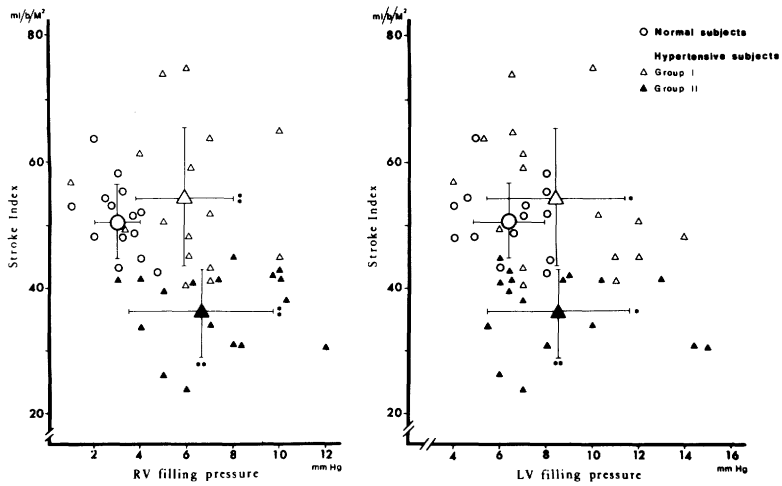

FIGURE 2. *Relationship between filling pressure and stroke index of the right and left ventricle in normal and hypertensive subjects. Averages (±SD) are indicated by the large symbols. * and ** indicate differences from the normal group significant at* $P < 0.05$ *and* $P < 0.01$, *respectively.*

ventricle, as evaluated through the variations in the mean rate of systolic ejection (R.MSEJR), was similar to the one of the left ventricle.

Figure 2 reports the relationship between stroke index and filling pressure of the right (end-diastolic pressure) and left ("a" wave in the pulmonary wedge pressure tracing) ventricles. This analysis provides further evidence that in hypertensive subjects both sides of the heart were involved in the same functional changes. In fact, in either side elevated filling pressures were associated with a somewhat augmented stroke index in group I, while comparable filling pressures were associated with a greatly reduced stroke index in group II.

Discussion

Pulmonary systolic, diastolic and mean wedge pressures were equivalent between the hypertensives, and significantly higher than in the normals. Age or somatic characteristics seem unrelated to such differences, because both were similar among the three groups.

Cardiac output was normal in group I and significantly reduced in group II; since the driving pressure across the lung was augmented in either group, pressure elevation in the pulmonary artery depended on an increased pulmonary arteriolar resistance.

Many factors are conceivably involved in a change in pulmonary arteriolar resistance; the major factors are of mechanical (pulmonary blood flow and volume, intrathoracic and alveolar pressures, back pressure from the left atrium and pulmonary veins) or vasomotor origin (respiratory gases, autonomic nervous system, catecholamines).[17, 18] Respiratory gases, pH of the blood and pulmonary blood volume do not seem to be responsible for an altered pulmonary vasomotility, because all of these variables were comparable between hypertensive and control subjects. Probably, blood flow was also unrelated to changes in pulmonary arteriolar resistance since it was normal in group I and reduced in group II, while pulmonary arteriolar resistance was elevated in either group. Pleural pressure, as estimated by an esophageal balloon during quiet regular respiration, was equivalent in the three groups; alveolar pressure was not determined, but no reason was seen for an increase in hypertensive patients. Therefore, extramural pressures can be excluded as important determinants of the differences in intraluminar pressure and arteriolar resistance between controls and hypertensives. Elevation in left ventricular end-diastolic pressure may well account for a rise in pulmonary arteriolar resistance. Recently, Atkins and coworkers[19] suggested that only a sustained elevation of back pressure from the left heart assumes increasing importance in determining pulmonary vascular resistance in hypertension. They found a high degree of correlation between pulmonary vascular resistance and wedge pressures greater than 20 mm Hg, but failed to see a relationship between the two parameters in subjects having a pulmonary wedge pressure lower than 20 mm Hg, although many of them presented an increased pulmonary vascular resistance. In our patients both pulmonary wedge pressure (fig. 1) and left ventricular end-diastolic pressure (fig. 2) were moderately elevated (lower than 20 mm Hg in each subject) and, in keeping with previous findings, were not related to the level of pulmonary vascular resistance. Pulmonary vascular resistance, in fact, was significantly higher in group II, while left ventricular filling pressure (fig. 2) was equal in the two hypertensive groups.

These considerations raise the possibility that the former variable was not fully dependent upon the latter. It should be remembered that all measurements were made at rest and that during normal activity the pulmonary wedge pressure could have been higher in the hypertensive groups, especially in group II. On the basis of the relationship existing between changes in systemic and pulmonary vascular resistance, an alternative explanation might be that a common mechanism produces vasoconstriction in the greater and in the lesser circulation.

Functional significance of the electrocardiographic alterations in hypertension, such as P wave changes,[20] T wave inversion in the left-sided leads,[21] criteria of left ventricular hypertrophy,[16, 20] has been investigated in several studies. Left ventricular hypertrophy was recognized to be associated with a compromised cardiac performance when both voltage and strain criteria were utilized to define hypertrophy.[20] Separation of voltage from strain criteria leads to different conclusions. In fact, in group I voltage increase was

associated with a significantly augmented thickness of the left ventricular posterior wall and interventricular septum, and some reduction in the internal minor axis at end diastole. Patients in this group likely had concentric hypertrophy of the left ventricle. In them cardiac muscle performance, as evaluated through the mean velocity of circumferential fiber shortening[14] was significantly and greatly enhanced compared to normal. Probably this was the mechanism that maintained or even increased the rate of ejection and the stroke index, in spite of augmented circumferential wall stress, pressure load and impedance to ejection. The output of the right side of the heart was normal and the rate of ejection augmented, even though pulmonary pressure and arteriolar resistance (and possibly wall stress and impedance to ejection) were greater than normal. These findings are in agreement with the documentation in animals of an enhanced right ventricular function following systemic hypertension-induced hypertrophy.[22] The reasons for increments in the filling pressures of both ventricles are not clear; at least as regards the left ventricle, a tentative explanation might be that concentric hypertrophy reduces ventricular compliance.

In group II, strain criteria of left ventricular hypertrophy were associated with increased left ventricular internal diameter and wall thickness. These patients presented a larger rise in pre-ejection afterload (CWS) and, probably, in impedance to ejection. In them, mean velocity of circumferential fiber shortening, mean rate of ejection, stroke and cardiac indexes, as well as the relationship between left ventricular filling pressure and stroke output, indicate a greatly reduced left ventricular performance. Coexistence of a significant impairment of right ventricular performance is documented by the elevated right ventricular filling pressure associated with a reduced stroke index.

These findings indicate that voltage and strain criteria of left ventricular hypertrophy have a well defined pathophysiological significance, and reflect different hemodynamic changes in the right and left ventricles, as well as in systemic and pulmonary circulations.

Although the present study was not designed to elucidate the basic mechanisms involved in the generation of the hypertensive cardiac disease, it may be postulated that in the presence of left ventricular pressure overload a stimulus is generated in response to the increased functional requirements of the myocardium. As suggested by Meerson,[23] this stimulus, which is maintained as long as the left ventricle is under stress, initially improves the function of the ventricle, but is subsequently overwhelmed by the adverse effects of direct exposure to an increasing stress. The pressure overload interpretation does not fit findings in the right side of the heart for two reasons: the right ventricle is exposed to only modest elevation of pulmonary arterial pressure; at equivalent levels of pressure loading its performance may be either enhanced (group I) or reduced (group II) in parallel with the performance of the left ventricle.

A functional interdependence of the two sides of the heart was documented in animals by Taylor and coworkers.[24] Cohn's studies in clinical shock[25] proved that these experimental principles can well influence the hemodynamic conditions in disease states such as acute myocardial infarction. The present study suggests that a chronic increase of left ventricular afterload may have important effects on the whole heart, and again proposes the concept that the right and the left sides represent a single functional unit. Although the nature of the signal that orchestrates the interdependence of the two ventricles remains undefined, their relationship in the same anatomical framework[26] can be regarded as a reasonable mechanism of interpretation.[25]

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