VOLUME-PRESSURE RELATIONS OF THE HUMAN PULMONARY
"VENOUS" SYSTEM STUDIED BY RADIONUCLIDE
ANGIOCARDIOGRAPHY AND PASSIVE LEG ELEVATION,
WITH SPECIAL REFERENCE TO THE EFFECT OF NITROGLYCERIN

SENRI HIRAKAWA, M.D., YUKIO OHSUMI, M.D., KOSHI GOTOH, M.D.
TAKAHIKO SUZUKI, M.D., HIDEKI FUJIWARA, M.D.
YASUO YAGI, M.D., AND HISATO TAKATSU, M.D.

In an attempt to clarify the effect of nitroglycerin (NTG) on the human pulmonary "venous" (P"V") system, short segments of volume-pressure (V-P) curves in the P"V" system were estimated in 50 patients before and after the sublingual administration of NTG. The pulmonary "venous" volume (P"V"V) was estimated with our own method, using radionuclide (RN) angiocardiology. The mean pulmonary artery wedge pressure ($\overline{PAW}$) was measured using a Swan-Ganz catheter. The increments of P"V"V and $\overline{PAW}$ that occurred during passive elevation of the legs were clues to the estimation of V-P "curves" in this system before and after NTG. In order to calculate a short segment of a V-P curve, the P"V"V was plotted on the ordinate and the $\overline{PAW}$ on the abscissa. In addition, we presented the effective unstressed volume graphically by extrapolating each short segment of V-P curves towards the volume axis (ordinate). We obtained the following results from the present study; (1) The sublingual administration of NTG caused the P"V"V- $\overline{PAW}$ -plots to shift to the left (-5.2 ± 3.6 mmHg, mean $\pm$ SD) and downwards (-19 ± 11 ml, mean $\pm$ SD). (2) The V-P curves appeared to shift to the left and become steeper after NTG. The average slope ($\Delta V/\Delta P$) was steeper after NTG (19.2 ± 11.3 ml/mmHg, mean $\pm$ SD) than before NTG (12.4 ± 7.9 ml/mmHg). (3) The graphically-obtained effective unstressed volume was unchanged with NTG, at least within the operating range of $\overline{PAW}$. (4) It is highly probable that NTG causes the tone of the P"V" system to be decreased by way of a relaxation of the vascular beds of the P"V" system.

NITROGLYCERIN (NTG) has been commonly used in clinical settings for the treatment of angina pectoris. Recently, many investigations

have been performed to clarify whether or not there would be a place for NTG in vasodilator therapy for patients with congestive heart failure!¹⁻³ It has been thought that the salutary effect of NTG for relieving congestive heart failure would result mainly from its vasodilating action on the systemic capacitance vessels, leading to the "systemic venous pooling" of the blood^{4,5} What is more important, the systemic

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The Second Department of Internal Medicine, Gifu University School of Medicine, Gifu, Japan

Mailing address: Senri Hirakawa, M.D., The Second Department of Internal Medicine, 40 Tsukasa-machi, Gifu 500, Japan

TABLE I PHYSIOLOGIC DATA, HEMODYNAMIC DATA AND EFFECTIVE UNSTRESSED DURING PASSIVE ELEVATION OF THE LEGS

Case No.	Age	Sex	Diagnosis	BSA (m ²)	CO (L/min)	PPT (second)	PBV (ml)	Elevation of the legs before NTG				
								$P''V''V$ (ml)	$\overline{PAW}$ (mmHg)	$\overline{\Delta V}$ (ml)	$\overline{\Delta P}$ (mmHg)	$\overline{\Delta V/\Delta P}$ (ml/mmHg)
1.	51	M	MI	1.64	4.80	8.2	505	354	12.3	25	1.9	13.2
2.	67	M	MI	1.52	4.20	8.7	469	328	9.8	21	4.2	5.0
3.	45	M	MI	1.81	3.93	10.1	509	356	7.5	45	2.7	16.7
4.	47	M	MI	1.68	4.70	8.4	507	355	7.6	78	3.2	24.4
5.	44	M	MI	1.47	6.88	5.0	441	309	3.1	29	1.8	16.1
6.	57	M	MI	1.78	4.61	8.0	473	331	6.5	37	2.5	14.8
7.	60	M	MI	1.72	5.31	6.5	443	310	6.5	34	3.0	11.3
8.	76	M	MI	1.42	5.92	5.7	433	303	8.4	51	2.2	23.2
9.	36	M	MI	1.69	5.09	6.8	450	315	9.7	27	3.2	8.4
10.	65	F	MI	1.30	3.62	7.4	344	241	9.6	28	4.3	6.5
11.	39	F	MI	1.45	4.66	6.0	359	251	6.0	22	2.5	8.8
12.	67	M	MI	1.44	4.07	6.9	360	252	2.1	33	7.3	4.5
13.	64	F	MI	1.47	4.28	7.0	384	269	6.3	39	3.7	10.5
14.	51	M	MI	1.53	5.04	5.5	356	249	6.9	37	3.5	10.6
15.	62	F	MI	1.41	3.50	6.8	305	214	7.5	23	2.9	7.9
16.	34	M	MI	1.42	4.69	7.8	466	324	21.3	18	1.9	9.5
17.	63	M	MI	1.54	5.24	7.6	511	358	25.4	21	5.6	3.8
18.	47	M	MI	1.66	5.02	8.7	560	392	14.7	25	8.1	3.1
19.	56	M	MI	1.73	5.33	8.5	581	407	13.0	31	8.9	7.9
20.	50	M	MI	1.52	6.43	6.5	536	375	15.9	40	6.2	6.5
21.	53	M	MI	1.62	3.64	11.5	537	376	21.1	23	3.9	5.9
22.	50	F	MI, MSR	1.29	2.72	11.4	398	279	20.4	13	3.9	3.3
23.	38	M	AP	1.68	5.66	6.8	494	346	8.4	58	2.8	20.7
24.	55	M	AP	1.64	4.83	7.4	459	321	5.0	27	2.3	11.7
25.	51	M	AP	1.62	4.95	6.9	438	307	6.1	33	2.4	13.8
26.	41	M	AP	1.68	4.83	5.7	353	247	5.0	35	2.3	15.2
27.	67	M	AP	1.59	4.14	7.2	383	268	8.5	28	3.7	7.6
28.	49	M	AP	1.60	5.47	5.5	386	269	4.9	19	2.4	7.9
29.	31	M	MS	1.58	4.81	11.6	716	501	11.4	51	1.8	28.3
30.	45	M	MS	1.82	6.37	7.8	639	447	5.9	71	3.1	22.9
31.	37	F	MS, AR	1.42	3.77	6.6	319	223	10.5	29	3.8	7.6
32.	60	F	MS	1.53	3.29	11.5	486	340	16.4	40	4.8	8.3
33.	53	F	MS	1.38	3.77	11.2	542	379	22.1	15	3.6	4.2
34.	54	M	NCA	1.64	6.86	5.9	518	363	5.3	60	1.5	40.0
35.	51	M	NCA	1.58	6.90	5.5	487	341	5.5	26	1.1	23.6
36.	37	M	NCA	1.65	6.14	6.4	511	358	6.8	49	1.8	27.2
37.	48	M	NCA	1.60	5.16	7.2	477	334	6.1	30	1.5	20.0
38.	70	M	DCM	1.60	3.33	14.2	607	425	7.7	66	3.3	20.0
39.	48	F	DCM	1.34	4.14	9.1	483	338	13.7	18	2.7	6.7
40.	66	F	DCM	1.39	2.99	8.0	311	218	19.8	24	6.4	3.8
41.	48	M	AR	1.71	7.18	4.7	433	303	3.9	34	2.1	16.2
42.	72	M	AR	1.39	3.00	12.1	466	326	7.8	34	4.3	7.9
43.	52	M	AR, MI	1.76	6.12	9.7	761	533	28.1	37	5.2	7.1
44.	54	M	HT	1.86	6.64	7.4	631	442	6.3	26	4.3	6.0
45.	43	M	HT	1.62	5.14	7.9	521	365	6.4	37	1.7	21.8
46.	52	F	HT	1.48	4.51	4.6	266	186	6.7	31	3.3	9.4
47.	66	F	HCM	1.40	3.57	6.8	316	221	4.6	30	4.0	7.5
48.	49	F	Myxoma	1.46	3.70	8.4	399	279	22.8	13	2.8	4.6
49.	52	M	MVR	1.46	4.69	6.8	409	286	4.7	35	2.3	15.2
50.	72	M	Pri.amy.	1.61	4.03	11.5	595	417	15.6	36	3.1	11.6
mean	53			1.56	4.79	7.9	467	327	10.4	34	3.3	12.4
±	±			±	±	±	±	±	±	±	±	±
S.D.	11			0.14	1.13	2.2	104	73	6.4	14	1.5	7.9

Abbreviations: BSA = body surface area
CO = cardiac output
PPT = peak to peak time
PBV = pulmonary blood volume
P''V''V = pulmonary "venous" volume

$\overline{PAW}$ = mean pulmonary artery wedge pressure
 $Vu.eff.$ = effective unstressed volume
MI = myocardial infarction
AP = angina pectoris
MSR = mitral stenosis plus regurgitation

VOLUME BEFORE AND AFTER ADMINISTRATION OF NTG SUBLINGUALLY

Sublingual administration of NTG				Elevation of the legs after NTG					Effective unstressed volume	
$\overline{PAW}$ (mmHg)	$-\Delta V$ (ml)	$-\Delta P$ (mmHg)	$-\Delta V/-\Delta P$ (ml/mmHg)	$P^{“V”}V$ (ml)	$\overline{PAW}$ (mmHg)	ΔV (ml)	$\overline{\Delta P}$ (mmHg)	$\Delta V/\Delta P$ (ml/mmHg)	$V_{u,eff.}$ (ml)	$V_{u,eff.NTG}$ (ml)
11.9	17	4.1	4.1	348	7.8	22	1.1	20.0	192	192
9.9	11	6.8	1.6	320	3.7	23	1.5	15.3	279	263
7.1	57	4.9	11.6	305	3.5	67	3.3	20.3	231	234
7.6	35	3.1	11.3	322	4.4	103	2.7	38.1	170	154
3.5	14	2.5	5.6	303	2.8	38	1.5	25.3	259	232
6.1	15	2.3	6.5	316	4.2	36	1.4	25.7	235	208
5.2	19	3.0	6.3	299	2.9	67	2.3	29.1	237	215
8.7	17	3.0	5.7	286	5.8	79	2.2	35.9	108	78
11.1	17	5.4	3.1	301	5.9	48	3.8	12.6	234	227
12.0	10	6.7	1.5	231	6.4	21	3.0	7.0	179	186
4.9	10	2.8	3.6	242	3.5	28	2.4	11.7	198	201
3.8	12	2.7	4.4	245	1.2	35	5.4	6.5	243	237
7.5	8	4.3	1.9	262	4.8	42	3.1	13.5	203	197
6.6	9	3.0	3.0	244	5.2	38	3.3	11.5	176	184
7.2	9	3.3	2.5	210	4.6	28	3.0	9.3	155	167
18.9	51	13.2	3.9	287	5.7	42	3.1	13.5	122	210
24.9	21	13.4	1.6	355	13.2	61	8.7	7.0	261	263
19.6	22	15.6	1.4	370	5.8	36	2.8	12.9	346	295
13.4	27	8.7	3.1	382	6.7	60	6.1	9.8	304	316
18.3	7	10.0	0.7	368	11.9	44	4.2	10.5	272	243
22.3	10	15.1	0.7	367	11.6	48	6.2	7.7	252	278
19.9	7	5.5	1.3	268	14.6	18	4.2	4.3	212	205
8.9	26	4.4	5.9	336	5.0	74	2.6	28.5	172	194
6.0	24	2.7	8.9	302	2.1	35	1.3	26.9	263	246
6.5	36	2.7	13.3	276	3.4	43	1.7	25.3	223	190
4.7	13	2.7	4.8	239	2.4	34	1.6	21.3	171	188
12.2	7	5.8	1.2	258	7.6	34	2.0	17.0	203	129
4.3	12	2.7	4.4	258	2.1	33	2.3	14.3	230	228
11.8	9	4.3	2.1	494	7.0	90	2.6	34.6	178	252
6.3	34	2.4	14.2	417	4.0	63	1.7	37.1	312	269
11.0	20	4.3	4.7	209	6.9	30	3.6	8.3	143	152
14.8	21	7.1	3.0	313	10.2	42	4.3	9.8	204	213
22.3	7	4.4	1.6	378	19.3	31	2.6	11.9	286	148
3.1	40	1.8	22.2	350	2.7	71	1.2	59.2	151	190
6.8	12	2.9	4.1	336	3.8	33	1.3	25.4	211	239
5.2	40	3.0	13.3	320	3.5	63	1.4	45.0	173	163
6.5	23	4.1	5.6	319	3.9	41	1.3	31.5	212	196
7.8	24	3.5	6.9	401	4.1	71	2.8	25.4	271	297
14.0	18	7.1	2.5	318	7.4	31	4.0	7.8	246	260
21.5	4	13.4	0.3	214	8.1	31	3.1	10.0	143	133
3.7	12	2.5	4.8	289	1.7	28	1.3	21.5	240	252
6.4	17	2.3	7.4	312	4.1	50	2.7	18.5	264	236
26.9	25	6.7	3.7	519	23.1	51	4.1	12.4	337	233
3.9	21	3.5	6.0	413	1.1	41	3.2	12.8	404	399
6.0	19	1.2	15.8	342	1.9	50	1.7	29.4	225	286
5.6	9	3.2	2.8	176	3.5	43	2.3	18.7	123	111
3.3	6	1.9	3.2	216	2.1	34	2.4	14.2	187	186
25.1	20	9.4	2.1	264	16.3	17	2.0	8.5	174	125
5.1	22	3.0	7.3	271	1.9	45	2.3	19.6	215	234
15.1	19	6.6	2.9	403	11.4	34	2.1	16.2	236	218
10.5	19	5.2	5.3	311	6.1	45	2.8	19.2	221	215
±	±	±	±	±	±	±	±	±	±	±
6.7	11	3.6	4.4	70	4.7	19	1.5	11.3	60	57

MS = mitral stenosis

AR = aortic regurgitation

DCM = dilated cardiomyopathy

HT = hypertension

NCA = neuro-circulatory asthenia

HCM = hypertrophic cardiomyopathy

MVR = status of mitral valve replacement

Pri.amy = primary amyloidosis

Four patients (No.34, 35, 36, 37) were regarded as normal cardiac function

Fig.1. The gamma camera was brought over the anterior chest and ROI was set at an area distant from the heart and liver.

Fig.2. Typical records of a study on chest radioactivity with leg elevation before and after the sublingual administration of nitroglycerin, showing the chest radioactivity (above) and the PAW (below). 38-year-old man, angina pectoris.

venous pooling of blood caused by NTG is considered to be a major factor in alleviating pulmonary congestion⁶. Actually, NTG has been found to directly dilate pulmonary vessels in animal experiments^{7,8}. However, little is known about the effects of NTG on the volume-pressure (V-P) relationship in the human pulmonary circulatory system. To our knowledge, the present study is the first one wherein the volume and pressure of human pulmonary "venous" (P"V") system were

estimated simultaneously.

By definition, the P"V" system consists of the pulmonary veins and left atrium. In the present study, we used our new method⁹ with a gamma camera and a Swan-Ganz catheter to estimate the short segment of V-P curves in the human P"V" system and to evaluate the effects of NTG on these curves. In addition, we estimated the effective unstressed volume of this system graphically from the short segment of V-P curves before

Fig.3. Illustrative case of P"V"V-PAW plots and their shift with elevation of the legs (LE), before and after the sublingual administration of nitroglycerin (NTG). 48-year-old man, normal control.

Fig.4. Volume-pressure relation of the ideal vessel and definition of slope compliance ($C = \Delta V / \Delta P$), extravolume, unstressed volume and effective unstressed volume.

and after sublingual administration of NTG in 50 patients with various cardiac diseases.

SUBJECTS AND METHODS

1) Subjects

Fifty patients, 37 men and 13 women, aged from 31 to 72 (53 ± 11 years old, mean $\pm$ SD) were studied. The underlying cardiac diseases are listed in Table I.

2) Methods

(1) Estimation of the pulmonary blood volume

Radionuclide (RN)-angiocardigraphy was performed with a gamma camera (Pho Gamma 4B and LFOV, Searle) equipped with a parallel hole ultra-high resolution collimator in left anterior oblique view by injecting ^{99m}Tc -pertechnetate in order to label the red blood cells in vivo in 46 cardiac patients and 4 control subjects.

For analysis of RN-angiocardigraphy, a data processing computer system (Scintipac 1200, Shimadzu Corp.) was used. It was possible to discretely monitor each of the components of the central circulation on the basis of visual identification of the anatomic sites. The details of our method to estimate the human pulmonary blood volume (PBV) have been previously reported elsewhere¹⁰ but the main points are reiterated in the Appendix. Finally, we estimated PBV from the pulmonary artery bifurcation (PAB) to the left atrium (LA) by equation (5), $\text{PBV} = \text{PPT}_{\text{large area}} \times 0.77 \times \text{CO}$, also described in the Appendix. CO was measured using a thermodilution method by Swan-Ganz catheter (93A-131-7F, Edwards Laboratories, Inc.).

(2) The calculation of the increment of PBV (ΔPBV) and mean pulmonary artery wedge pressure (ΔPAW) by passive elevation of the legs

After radioactivity had reached equilibrium in the circulating blood, a lead plate with a hole at its center was placed over the right middle anterior chest removed as far as possible from the liver and the heart. The region of interest (ROI) of the gamma camera was set over this hole in the lead plate (Fig. 1). The radioactivity of ROI were counted every 30 seconds for several minutes. After the counts of radioactivity became nearly stable, both legs of each patient were elevated passively at 30 degrees for 3 min.

By definition, P"V"V was 70% of PBV and an increment in P"V"V ($\Delta\text{P"V"V}$), caused by elevation of the legs, was 80% of ΔPBV . The figure 70% was derived from Burton's data¹¹ and the figure 80% was based on our previous study¹² in which the ratio of compliance of the P"V" system to that of the pulmonary arterial system was investigated. Since it is impossible to determine the pulmonary arterial volume and P"V"V separately, we assumed in the present study that the percentage distribution of PBV to the P"V" system and percentage increase of the volume in

Fig.5. The illustration expresses the effective unstressed volume before ($V_{u,eff.}$) and after ($V_{u,eff.NTG}$) the sublingual administration of nitroglycerin obtained graphically by extrapolating each short segment of V-P curve towards the volume axis. Each straight line shows the short segment of V-P curve and each dotted line shows its extrapolation towards the volume axis in human P-V system 67-year-old man, with old myocardial infarction.

the P-V system would be unchanged when the PBV was increased with LE before and after NTG administration. The $\Delta P-V$ was calculated using the equation (10), $\Delta P-V = (1/0.8) \cdot PBV \cdot (R_{LE} - R_O)/R_O$, (in Appendix). The details of our method to estimate the PBV are shown in Appendix, equations (1) to (5).

The ΔPAW was determined as follows: PAW was recorded using a previously introduced Swan-Ganz catheter, and ΔPAW during elevation of the legs was measured as shown in Fig. 2.

(3) Effect of NTG on the P-V system

After the passive elevation of the legs was repeated 2 times to ascertain reproducibility, and the counts of the radio-activity over the right chest and PAW reached the stable state, NTG (0.3 to 0.6 mg) was administered sublingually. The chest radio-activity and PAW were decreased after sublingual administration of NTG. At the end of 6 to 9 min after NTG administration, when the action of NTG was considered to be great enough, the passive elevation of the legs was repeated again. Data are shown in Fig. 2.

(4) V-P curves of the P-V system

The V-P plots of the P-V system are constructed by indicating the P-V-V on the ordinate against the PAW on the abscissa, in such a way as shown in Fig. 3. The point A indicates the V-P plot obtained at rest in a supine position and the point B indicates the V-P plot during the passive elevation of the legs. The slope ($\Delta V/\Delta P$) of the line constructed by connecting points A and B represents the compliance, i.e., C_{LE} .

The line connecting A and B can be regarded as a short segment of the V-P curve in the P-V system. On the other hand, the point C was obtained at rest in a supine position after sublingual administration of NTG. As can be seen, the point C was located to the left and downward to the point A. The passive elevation of the legs resulted in a change of point C to point D. The slope ($\Delta V/\Delta P$) of the line constructed by connecting the points C and D represents the compliance of the P-V system after NTG, i.e., C_{LE-NTG} .

(5) Effective unstressed volume of the P-V system

Unstressed volume (V_u) is defined as the volume-axis-intercept of the V-P curve and is

Fig.6. $P''V''V$ -PAW-plots and their shift with elevation of the legs or sublingual administration of nitroglycerin (NTG).

Fig.7. $P''V''V$ -PAW-plots and their shift with elevation of the legs, before and after the sublingual administration of nitroglycerin (NTG).

shown in Fig. 4. It is impossible to measure the true unstressed volume directly in the human P"V" system. However, the effective unstressed volume ($V_{u,eff.}$) can be estimated in humans, as shown in Fig. 4, by determining the volume intercept of the extrapolated tangent line drawn

at the point A. The illustrative case was shown in Fig. 5.

RESULTS

(1) Effect of NTG on the P"V" system

Fig. 8. Effective unstressed volume in human pulmonary venous system before and after the administration of nitroglycerin (NTG).

As can be noted in Fig. 3, P“V”V-PAW plot and its shift ($\Delta V/\Delta P$) with passive elevation of the legs (LE) in the absence of NTG allowed us to estimate a short segment of the V-P curve of the P“V” system. The short segments of the V-P curves were obtained from 50 patients with various cardiac diseases, and were constructed by plotting the P“V”V on the ordinate against the PAW on the abscissa. Then, sublingual administration of NTG at doses of 0.3–0.6 mg caused the P“V”V-PAW plots to be shifted to the left and nearly horizontally (-5.2 ± 3.6 mmHg, mean $\pm$ SD), but downwards (-19 ± 11 ml, mean $\pm$ SD) in all patients (Fig. 6).

Next, the short segment of the V-P curves in the P“V” system was obtained after NTG in all the cases of 50 patients (Fig. 7).

The slope of the V-P curves in this system, that is, compliance, averaged 12.4 ± 7.9 ml/mmHg (mean $\pm$ SD) before NTG, while it was 19.2 ± 11.3 ml/mmHg after NTG ($p < 0.001$), indicating that the compliance of the human P“V” system increased with NTG.

(2) Effect of NTG on the effective unstressed volume of the P“V” system

The effective unstressed volume was obtained graphically before and after the sublingual administration of NTG in 50 patients (Fig. 8). The effective unstressed volume was 221 ± 60 ml (mean $\pm$ SD) before NTG and 215 ± 57 ml after NTG, respectively ($V_{u.eff. NTG} - V_{u.eff.} = -6 \pm 38$ ml and coefficient of variation = $\pm 18\%$), indicating that the effective unstressed volume was nearly the same before and after NTG, although variations were seen to some extent. All the data related to the effective unstressed volume obtained in the present study are presented in Table I.

DISCUSSION

(1) Stability of the measurements of the PBV

The short segment of the V-P curves in the human P“V” system before and after NTG were estimated under an assumption that PBV remained unchanged throughout the study. For Fig. 2,

for instance, PBV was assumed to remain constant at three points in time; (1) zero time; (2) soon after the first two measurements of passive elevation of the legs; and (3) after the end of the study, about 50 min after. In 9 patients in this study, PBV was estimated in duplicate at the points of time zero and after the end of the experiments (about 100 minute's duration) using the equation (5) shown in the Appendix. As a result, PBV averaged 452 ± 93 ml (mean $\pm$ SD) at the time zero and 451 ± 94 ml at the end of the experiments. The variation of the estimated PBV, i.e., final minus initial, was -1 ± 35 ml (mean $\pm$ SD), and the coefficient of variation was $\pm 8\%$, indicating that PBV remained reasonably constant enough to allow us to use the initial value of PBV for calculation of the P"V"V by equation (10) in the Appendix.

(2) Validity of method to calculate the compliance ($\Delta V/\Delta P$) of the human P"V" system

We calculated the compliance of the human P"V" system as $\Delta P"V"V/\Delta \overline{PAW}$, that is, equation (11) shown in the Appendix. We have developed a method to calculate the compliance ($\Delta V/\Delta P$) of the human P"V" system, different entirely and independent from that described heretofore in the present study. It is based on the analysis of the PAW pressure tracings (C_{PAW}).¹³⁻¹⁵ Therefore, we applied these two entirely different and independent methods simultaneously in 40 patients. It was found that, in the absence of NTG, the compliances estimated from both methods were fairly similar ($C_{PAW} = 0.76 C_{LE} + 4.6$, $r = 0.76$, $p < 0.01$, $n = 40$ ¹⁶). It suggests that the both methods are valid in estimating the compliance of human P"V" system.^{17,18}

(3) V-P relation of the human P"V" system

Okada et al.¹⁹ have reported that in the equilibrium phase of RN-angiocardiology, exercise caused the count of radioactivity from the pulmonary field to be increased significantly in patients with ischemic heart disease when compared to normal subjects. Therefore, they have stressed the importance of counting the radioactivity from the pulmonary field during exercise when making a diagnosis of ischemic heart disease. In addition to this, Tubau et al.²⁰ found that the mechanism responsible for the increase in the counts of radioactivity over the lung field in response to exercise or atrial pacing would be the elevation of the pulmonary artery

wedge pressure. However, they examined only the increase in PBV semi-quantitatively from the RN activity over the lung. In the present study, we obtained the "absolute" value of the PBV from equation (5) and P"V"V from equation (10) as shown in the Appendix, together with the measurement of $\overline{PAW}$. Our present study represents a new quantitative approach to examine the V-P relation of the P"V" system in human.

(4) Effect of NTG on the human P"V" system

There have appeared numerous reports^{21,22} on the effects of NTG on the PBV. Many investigators^{7,8} have reported that in animal studies, NTG acts directly on the pulmonary vascular system. However, to our knowledge, only a few data²³ have proved such an action of NTG in human subjects. Ferrer et al.²⁴ described in their human study that the sublingual administration of NTG caused the PBV to be increased. On the other hand, Schneider et al.²⁵ reported that NTG hardly affected the PBV and Slutsky et al.²⁶ reported that NTG caused a decrease in PBV. In the present study, the sublingual administration of NTG caused the PBV and P"V"V to be decreased or unchanged, together with a decrease in the $\overline{PAW}$ in all cases (Fig. 6). For instance, it is demonstrated in Fig. 5 that the P"V"V fell slightly by the sublingual administration of NTG.

In addition, the slope ($\Delta V/\Delta P$) of a short segment of V-P curve, constructed by connecting the two V-P plots one obtained before the passive elevation of the both legs, and the other obtained during the passive elevation of legs was significantly steeper in the presence of NTG than in the absence of NTG ($p < 0.001$) (Fig. 7). The slope ($\Delta V/\Delta P$) was 12.4 ± 7.9 ml/mmHg (mean $\pm$ SD) before the administration of NTG and 19.2 ± 11.3 ml/mmHg after the administration of NTG. Therefore, it is suggested that, with NTG, V-P curves of the P"V" system shift to the left side, occupying the position of steeper (more compliant) curves.

(5) Effective unstressed volume

Generally, unstressed volume cannot be measured directly under normal physiological conditions. However, the effective unstressed volume can be projected from the point of intersection of the tangent line drawn at the operating point on the V-P curves extrapolated towards the volume axis, using the method of Beneken.²⁷ The values of the effective unstressed volume

obtained graphically by our method were found to be almost the same before and after administration of NTG²⁸ at least within the operating range of PAW. Guyton²⁹ produced simulation models of the circulatory system, and assumed that the V-P relation of the P"V" system could be regarded as a straight line within the operating range of pressure. Effective unstressed volume was considered to be constant. The findings obtained in the present study seems to support the validity of their model.

At present, vasodilators are classified roughly into three types according to their effects on the systemic resistance and capacitance vessels, i.e., those which act on the systemic resistance vessels, those which act on the systemic venous system and those which act on both the systemic resistance and capacitance vessels. On the basis of this classification, vasodilators have been used properly aiming at afterload or preload reduction. However, the presence of the P"V" system as a reservoir of the left ventricle (LV) makes it difficult to judge whether or not the effects of vasodilators on the venous system stands for directly the effects of those on the preload of LV. It is, therefore, important to evaluate the effects of vasodilators on the P"V" system for the purpose of evaluating the effects of those on the preload of LV.

In the present study, we found that NTG caused the preload of LV to decrease through its direct action on the P"V" system, and it seems essential to clarify the effects of other vasodilators on the P"V" system in order to evaluate the left ventricular preload reducing action of vasodilators.

In conclusion, it is probable that the administration of NTG causes a shift of V-P curve in the P"V" system towards the position of P"V" system with reduced tone, without changing the effective unstressed volume. It was thus shown that the administration of NTG produced not only the dilation in the systemic veins but also the venodilation of the P"V" system.

APPENDIX

Derivation of our formulae, described in this paper, is as follows:

First, using a data processing computer system, radionuclide dilution curves were obtained externally at the regions of the pulmonary artery bifurcation (PAB) and the left atrium (LA). Injection was performed into the right atrium.

From the difference in the mean transit time (MTT) between PAB and LA ($\Delta\text{MTT}_{\text{PAB-LA}}$) and cardiac output (CO), the pulmonary blood volume (PBV) which exists between PAB and LA was calculated as,

$$\text{PBV} = \Delta\text{MTT}_{\text{PAB-LA}} \times \text{CO} \dots\dots\dots (1)$$

When time activity curve of the LA could not be obtained satisfactorily from RN imaging, peak to peak time (PPT) in the time-activity-curve, obtainable over a large area almost covering the entire heart, was used for the measurement of PBV by equation (5), which is the result of our previous study.¹⁰ To recapitulate the main points, the difference in the MTT between PAB and left ventricle (LV) ($\Delta\text{MTT}_{\text{PAB-LV}}$), between right ventricle (RV) and LA ($\Delta\text{MTT}_{\text{RV-LA}}$) and between RV and LA ($\Delta\text{MTT}_{\text{RV-LA}}$) were calculated and these were compared in terms of the time relationship to the PPT. We obtained the time relationship of equation (2), empirically from 46 patients with cardiac or noncardiac diseases.

$$\Delta\text{MTT}_{\text{PAB-LV}} = \text{PPT}_{\text{larger area}} \dots\dots\dots (2)$$

We also obtained the same empirical time relationship of equation (2) from mechanical experimental models of cardiopulmonary circulation.³⁰ Another time relationship equation (3) was obtained empirically from 24 patients. That is,

$$\Delta\text{MTT}_{\text{PAB-LA}} = \Delta\text{MTT}_{\text{PAB-LV}} \times 0.77 + 0.05 \dots\dots\dots (3)$$

where the last term (0.05) was small enough to be neglected.

From equations (2) and (3), we may write, for human subjects,

$$\Delta\text{MTT}_{\text{PAB-LA}} = \text{PPT}_{\text{larger area}} \times 0.77 \dots\dots (4)$$

Parenthetically, the time relation in equation (4) was in agreement with the actual time relationships, found in anesthetized open-chest dogs.

From equation (1) and (4), we may write

$$\text{PBV} = \text{PPT}_{\text{larger area}} \times 0.77 \times \text{CO} \dots\dots (5)$$

Our method to estimate the increment in PBV in response to the passive elevation of the legs can be expressed, first, by equation (6)

$$\Delta\text{"PBV"} = (1/m) \cdot \text{PBV} \cdot (R_{\text{LE}} - R_{\text{O}}) / R_{\text{O}} \dots\dots\dots (6)$$

where R_{O} represents the radioactivity (counts) over the right chest wall at rest and R_{LE} the

radioactivity over the same right chest wall during leg elevation (LE).

The correction factor, m , was determined to eliminate contamination from the radioactivity of the anterior and posterior chest wall origin. We may write

$$m = (R - (R_A + R_P))/R \dots \dots \dots (7)$$

where R represents the radioactivity of the middle chest field (including anterior and posterior chest walls) obtained by single photon emission computed tomography (SPECT), R_A the radioactivity of the anterior chest wall obtained by SPECT and the R_P the radioactivity of the posterior chest wall obtained by SPECT. Each radioactivity was measured from the sagittal view of SPECT at the equilibrium phase of radionuclide.

With this method, the value of m obtained from 10 patients with various cardiac diseases was found to be

$$m = 0.83 \pm 0.04 \text{ (mean } \pm \text{ SD) which was very close to 0.8.}$$

Therefore, we may write

$$\Delta \text{"PBV"} = (1/0.8) \cdot \text{PBV} \cdot (R_{LE} - R_O)/R_O \dots \dots \dots (8)$$

To examine another correction factor, attenuation by chest wall and lung water, we performed experiments with mechanical model. As a result, we found that the calculated increment in volume of the "lung" was about 80% of the actual increment in volume. With this correction factor (0.8), we may rewrite equation (8) as,

$$\Delta \text{PBV} = (1/0.8) \cdot (1/0.8) \cdot \text{PBV} \cdot (R_{LE} - R_O) / R_O \dots \dots \dots (9)$$

By definition, an increment in the pulmonary "venous" volume ($\Delta \text{"V"}V$), caused by elevation of the legs, was 80% of ΔPBV .

Therefore, our final equation was

$$\Delta \text{"V"}V = (1/0.8) \cdot \text{PBV} \cdot (R_{LE} - R_O)/R_O \dots \dots \dots (10)$$

The slope compliance ($\Delta V/\Delta P$) is given as

$$(\Delta V/\Delta P)_{\text{slope}} = \Delta \text{"V"}V/\Delta \text{PAW} \dots \dots (11)$$

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