Diagnosis of Tricuspid Regurgitation by Contrast Echocardiography

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SUMMARY Sixty-two subjects underwent M-mode and two-dimensional echocardiographic studies that included imaging of the inferior vena cava (IVC) during upper extremity contrast injections. Group 1 consisted of 10 patients with clinical tricuspid regurgitation (TR). Group 2 consisted of 40 patients without definite clinical signs of TR but with conditions known to be commonly associated with TR (e.g., mitral valve disease, pulmonary hypertension, former tricuspid valve surgery). Group 3 consisted of 12 normal subjects. The IVC could be imaged by two-dimensional echocardiography followed by M-mode in all subjects. M-mode IVC measurements in the absence of contrast were not sufficient to reliably separate TR patients from non-TR patients. IVC contrast was imaged, frequently during deep inspiration, in all 10 group 1 patients, 36 of 40 group 2 patients and three of 12 group 3 normal subjects. Three patterns of contrast appearance in the IVC were observed: "v-wave synchronous" patterns in all but two patients with TR and "a-wave synchronous" or "random" patterns in patients without TR. The presence of TR was independently assessed during angiography or surgery in 26 patients. There were two false-negative echo studies, as judged by intraoperative palpation of a thrill on the right atrium. There were no false-positive v-wave synchronous studies. M-mode echocardiography was superior to two-dimensional echocardiography in detection of the appearance of contrast in the IVC and ease of pattern interpretation. Recognition of false-positive (a-wave synchronous or random) and false-negative patterns (insufficient central contrast, excessively inferior transducer position) improves the diagnostic accuracy of contrast IVC echocardiography, which is a sensitive and specific method for diagnosing TR.

LIEPPE et al.[1] recently suggested that two-dimensional echocardiography is a sensitive and specific means for diagnosing tricuspid regurgitation (TR). They used ultrasound contrast from an antecubital vein injection of saline or indocyanine green, and monitored the inferior vena cava (IVC) for appearance of contrast from the subcostal transducer position. We noted appearance of contrast in the IVC with this technique in several patients without TR, and undertook a study to examine the sensitivity and specificity of contrast echocardiography for the diagnosis of TR. We also examined the relative usefulness of M-mode and two-dimensional echocardiography in diagnosing TR.

Methods

Patients

Sixty-two patients underwent M-mode and two-dimensional echocardiography with peripheral contrast injections. Each patient was examined by a car-

diologist, with particular attention to the jugular venous pulse, the presence or absence of a murmur consistent with TR, hepatic pulsations and peripheral edema. Patients were divided in three groups with respect to the clinical assessment of the presence or likelihood of TR.

Group 1 included 10 patients with a definite clinical diagnosis of TR, based on a prominent jugular systolic pulsation, a holosystolic murmur that increased with respiration (Carvalho's sign), and a pulsating liver on palpation. Three of these patients had right ventricular angiograms and two underwent cardiac surgery; TR was present in all five. Group 2 included 40 patients who did not have clinical TR but had cardiac disorders frequently associated with TR, such as rheumatic mitral stenosis, pulmonary hypertension, and status post tricuspid valve repair or replacement for TR. Most of these patients had atrial fibrillation and systolic murmurs of nontricuspid origin, rendering clinical assessment of the tricuspid valve difficult. Twenty-one of these patients had operations or right ventricular angiograms: 10 had no TR and 11 had TR. Group 3 included 12 subjects who were normal by history, physical examination and M-mode and two-dimensional echocardiograms.

Angiographic and Operative Diagnosis of Tricuspid Regurgitation

The presence of TR was diagnosed from right ventricular angiograms if contrast appeared in the right atrium in the absence of premature complexes. Intra-

operative diagnosis of TR was made if a thrill was present upon right atrial palpation before cannulation for cardiopulmonary bypass.

Echocardiographic Methods

Patients were studied in the supine position with slightly flexed knees and hips to allow better relaxation of the abdominal musculature when the subcostal transducer position was used. The IVC was visualized in the sagittal plane by means of two-dimensional echocardiography during the initial three to five contrast injections, with M-mode IVC imaging during later injections. Two-dimensional contrast echocardiograms were also recorded from the left sternal border and apical transducer positions with the patient in the partial left lateral decubitus position.[2, 3] M-mode echocardiograms were obtained with an EchocardioVisor SE (Organon Teknika) interfaced to a Honeywell LS6 strip-chart recorder. Two-dimensional echocardiograms were recorded with an EchocardioVisor 03 (Organon Teknika) multielement, linear-array scanner or a Toshiba SSH-10A phased-array sector scanner and stored on videotape for subsequent analysis. Gain, reject and damping settings on both instruments were adjusted to display the IVC cavity just at the threshold where noise is seen. Microbubbles, the source of contrast effect,[4] are strong reflectors and can usually be differentiated from noise by their characteristic motion patterns.

Echocardiographic contrast was obtained by rapidly injecting 5–8 ml of 5% dextrose in water (D5W) into an upper extremity vein through a three-way stopcock and a #18- or #19-gauge butterfly needle or plastic catheter. To ensure adequate contrast, 1–3 ml of medically pure (100%) carbon dioxide (CO_2) were added to 4–6 ml of D5W to create an improved ultrasonic contrast agent.[5] This was done for three to 10 injections after the initial one or two injections of D5W alone in the first 49 patients studied. The mixture was prepared and agitated just before each injection to increase the contrast content of the venous blood. When connecting and agitating the mixture of CO_2 and D5W in the syringe, we were careful to hold the syringe so the CO_2 could never mix with room air. Subcostal IVC imaging during contrast injection was performed during quiet respiration, deep inspiration and Valsalva maneuver in each patient.

IVC dimensions were calculated using the leading-edge method from the mean of three measurements at (1) the onset of QRS on the simultaneously recorded ECG, (2) the minimal diameter in early systole before the onset of the "v" wave, and (3) the maximal diameter during the "v" wave (fig. 1). With this method, the minimal diameter after the "a" wave and the peak "v" wave maximal diameter are measured. The percentage of systolic pulsation was calculated using the formula ([maximal dimension − minimal dimension]/minimal dimension) × 100. Two groups were compared with respect to differences in IVC measurement: a definite TR group and a non-TR group. The TR group included 21 patients — all 10 in group 1 with clinical TR, plus 11 additional group 2 patients with an angiographic or intraoperative diagnosis of TR. The non-TR group of 22 subjects in-
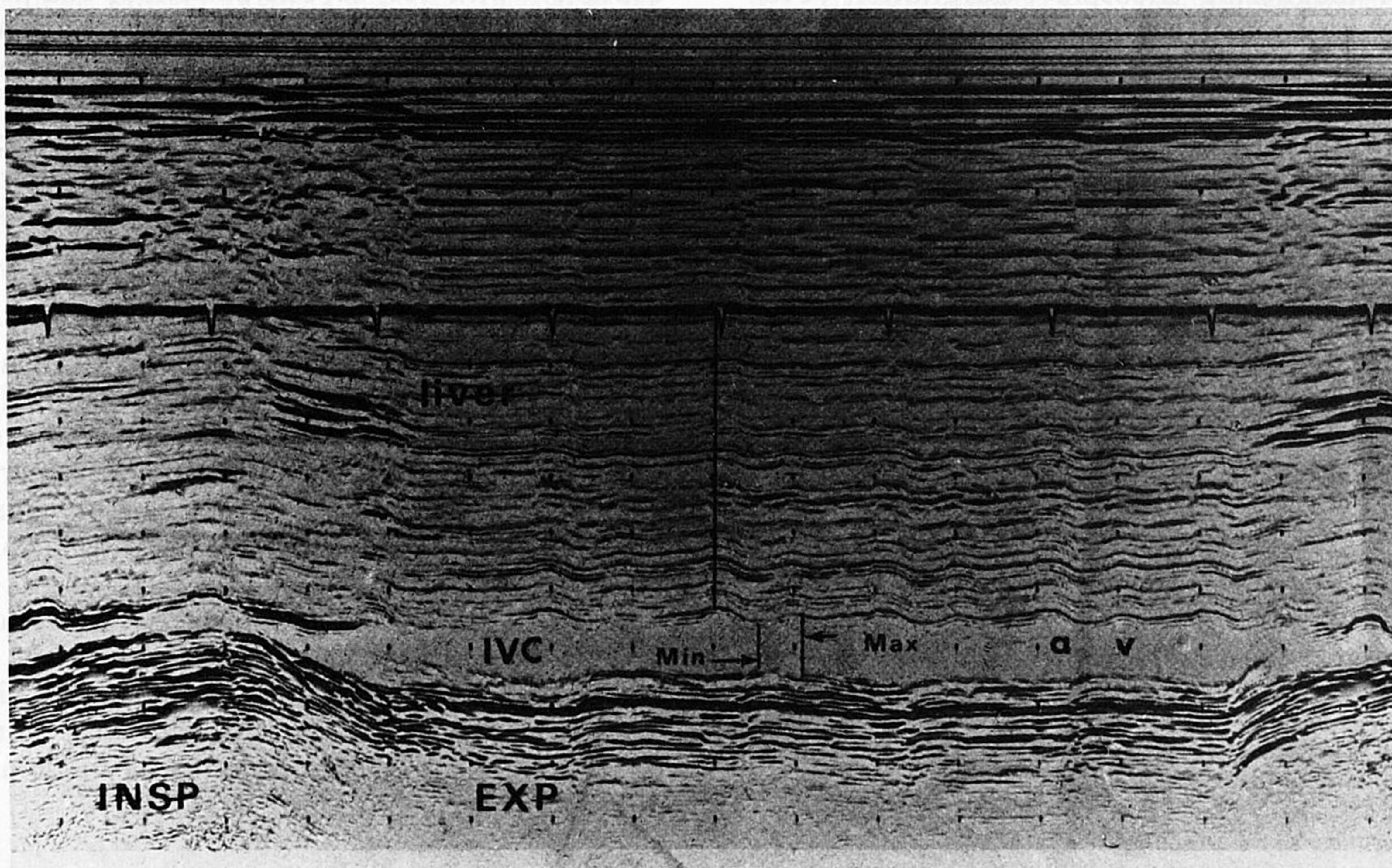

FIGURE 1. *Normal M-mode inferior vena cava (IVC) echocardiogram showing how measurements were made. IVC dimensions were measured at the onset of the QRS, minimal systolic dimension before onset of the "v" pulsation (Min) and maximal dimension during the "v" pulsation (Max). INSP = inspiration; EXP = expiration; a = "a" pulsation; v = "v" pulsation.*

TABLE 1. *Inferior Vena Cava Dimensions*

| Group	D-QRS	D-min	D-max	% systolic pulsation
TR	23 ± 4	23 ± 4	24 ± 4	3 ± 6
	n = 21	n = 21	n = 21	n = 21
Non-TR	18 ± 3	16 ± 5	18 ± 4	12 ± 13
	n = 10	n = 16	n = 20	n = 20
p	< 0.001	< 0.001	< 0.001	< 0.02

Measurements are given as mean ± SD.

Abbreviations: D-QRS = IVC diameter at QRS onset (in mm); D-min = IVC minimal diameter in early systole before onset of "v" wave; D-max = IVC dimension at maximal "v" wave; n = number of subjects with tracing of sufficient quality to perform measurement; p = p value of unpaired t tests between the groups listed.

cluded the 12 normal subjects in group 3, nine group 2 patients with negative intraoperative palpation for TR and one group 2 patient with a negative right ventricular angiogram.

Results

IVC size and Pulsation

The IVC was adequately visualized by both M-mode and two-dimensional echocardiography in all patients. Patients with TR had a larger IVC dimension than those without TR (table 1). This was statistically significant for measurements made at QRS onset at the minimal dimension before the "v" wave, or at the maximal dimension during the "v" wave. However, there was considerable overlap between the groups, so IVC dimension alone cannot differentiate between patients with and those without TR. Patients with IVC dimension at QRS onset, or maximum "v" pulsation, of greater than 24 mm all had TR, and none of those with dimensions less than 16 mm had TR. However, most patients in this study had IVC dimensions of 16–24 mm. The percentage of systolic pulsation was higher in the non-TR group, but the large overlap precluded using this test to predict the presence of TR in individual patients.
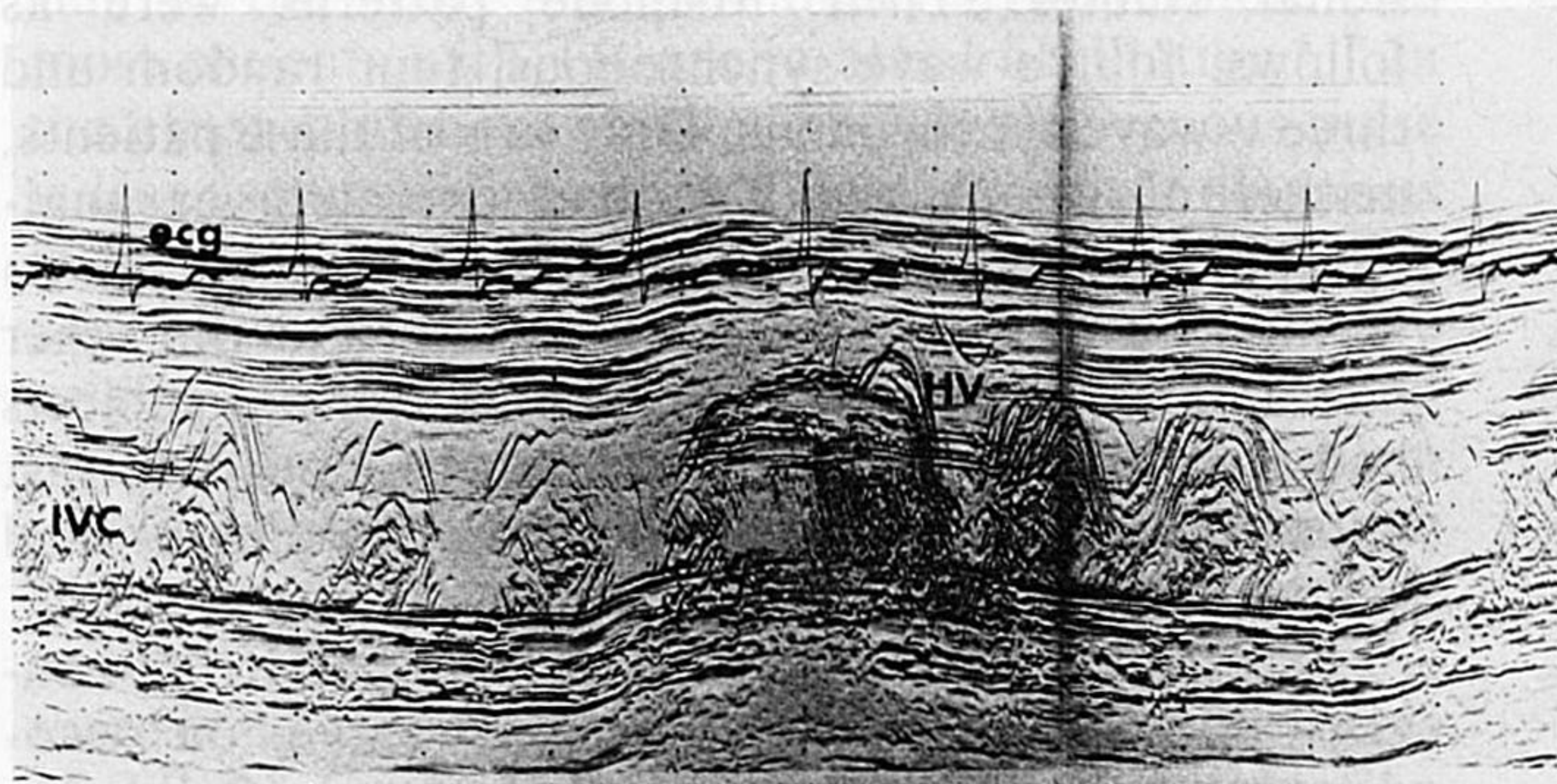
Patterns of IVC Contrast Appearance

No side effects from contrast injections were noted. Contrast was detected in the IVC on M-mode examination in all patients in group 1, 36 of 40 patients in group 2 and three of 10 normal subjects in group 3. Different patterns of IVC contrast appearance were noted. Figure 2 is an example of the echo pattern in patients with TR. The appearance of contrast in middle and late systole is indicated by upward-slanting lines. The lines slant upward because the contrast is moving inferiorly and approaches the superiorly aimed transducer. The contrast then reverses direction and returns toward the heart during diastole, producing downward-sloping lines. This is the most common pattern seen in TR. The timing of the appearance of contrast in the IVC is neither predominantly systolic nor predominantly diastolic, but coincides with the "v" wave of the right atrial pressure tracing or the jugular venous pulse. Therefore, this pattern was termed "v-wave synchronous." An example of a two-dimensional echocardiogram from a patient with TR is shown in figure 3.

A false-positive pattern is shown in figure 4. Contrast appears in the IVC during the "a" wave of the jugular venous pulse tracing and is thus due to atrial contraction rather than TR. A more subtle false-positive pattern is shown in figure 5, in a patient with no palpable TR at operation. In this pattern, appearance of contrast is influenced by respiration but has no clear relation to the cardiac cycle, and was therefore designated the "random" pattern.

Distribution of Echo Patterns (table 2)

All 10 patients in group 1 with clinical TR had a v-wave synchronous pattern of echocardiographic con-

TABLE 2. *M-mode Inferior Vena Cava Echo Patterns*

Group	V-wave synchronous	A-wave synchronous	Random	No contrast
1 (n = 10)	10	0	0	0
2 (n = 40)	20	9	7	4
3 (n = 12)	0	3	0	9

FIGURE 2. *M-mode contrast inferior vena cava echocardiogram showing a v-wave synchronous pattern typical for tricuspid regurgitation. Note the increased contrast effect due to inspiration in the middle of the figure. All of the contrast in the hepatic vein (HV) and most of the contrast in the IVC has an upward slope during the early part of systole, indicating retrograde flow coming toward a superiorly directed transducer, and a negative slope as the contrast returns towards the heart during the latter part of the v-wave, in early diastole.*
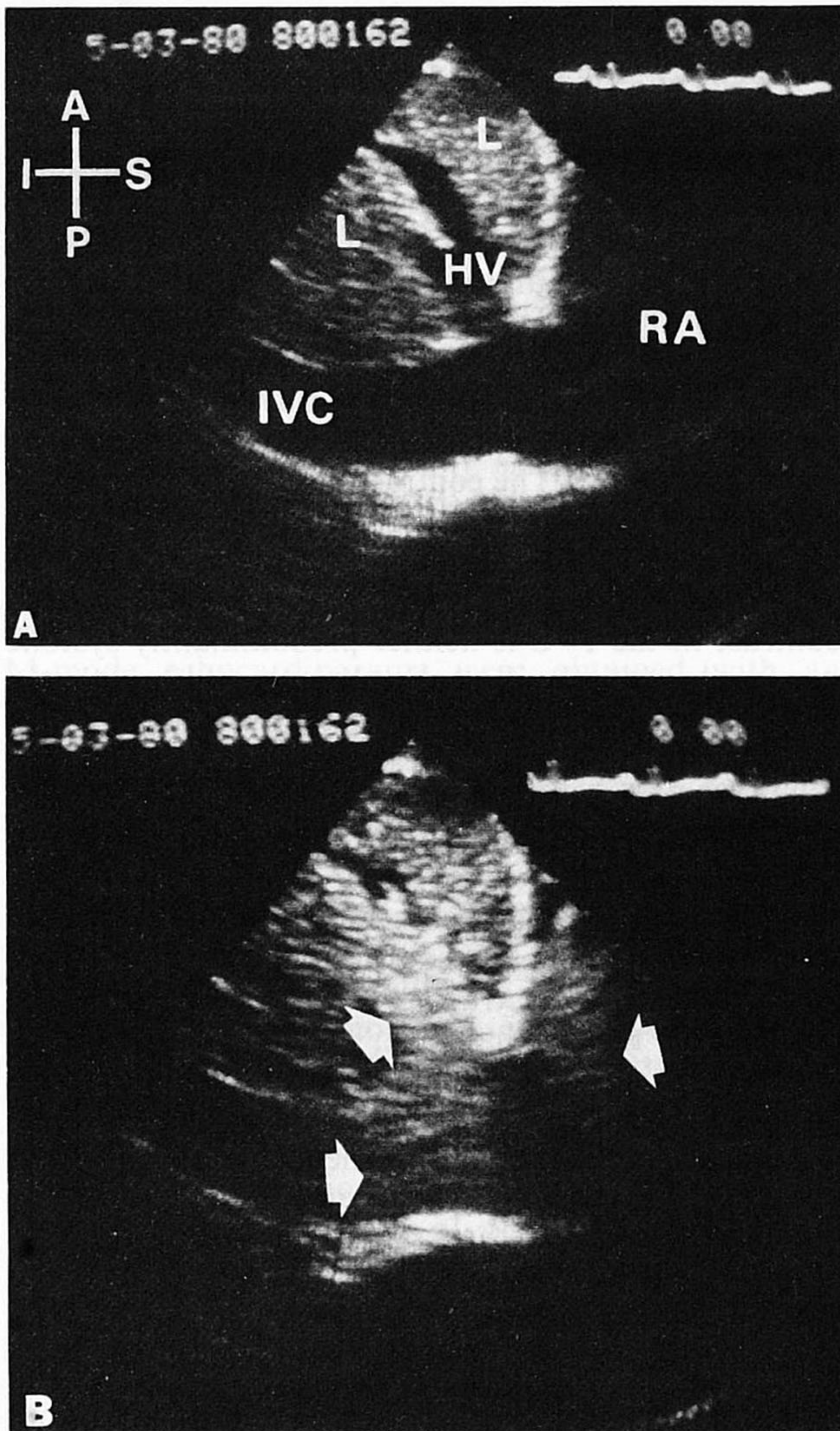
FIGURE 3. *Stop-frame photographs from a subcostal two-dimensional echocardiographic study of the inferior vena cava (IVC) and right atrium (RA) before (A) and immediately after (B) upper extremity injection of 5% dextrose in water. The IVC and hepatic vein (HV) fill with contrast (arrows) in this patient with tricuspid regurgitation later proved by intraoperative right atrial palpation. L = liver; A = anterior; P = posterior; I = inferior; S = superior.*

trast appearance in the IVC (fig. 2). Five of the 10 patients had right ventricular angiograms or intraoperative right atrial palpation in close temporal proximity to their echocardiographic study and TR could be confirmed by these independent means in all five. Two of the 12 normal subjects in group 3 had IVC echocardiographic contrast on their M-mode study but not on the two-dimensional IVC echocardiogram and another group 3 patient had it on both. In all three, contrast appeared at end-inspiration only. None of the group 3 subjects had contrast in the IVC during normal quiet respiration.

Of the 40 patients in group 2, 20 had v-wave synchronous IVC echo patterns suggesting TR. Several of these were seen only near the end of inspiration; none of the patients with isolated late-inspiratory v-wave

synchronous patterns had operation or right ventricular angiography to verify the presence or absence of TR. Ten group 2 patients had a-wave synchronous IVC contrast patterns, indicating the absence of TR. Seven group 2 patients had a random pattern of echo appearance: All of these studies showed strong inspiratory variation in IVC contrast. The last four group 2 patients had no IVC contrast.

Confirmation of Echo Patterns

Twenty-six of the study subjects had either right ventricular angiograms or right atrial palpation at operation to verify the presence of TR. Sixteen of the studies were positive for TR, and 14 of these 16 patients had v-wave synchronous IVC contrast during normal respiration. The last two had no IVC contrast appearance even though a thrill was detected during intraoperative right atrial palpation. These were the only two false-negative echo studies. Of the 10 patients with normal tricuspid function at angiography or operation, five had a random appearance of contrast unrelated to "a" or "v" waves, and four showed contrast during the "a" wave only. These four were the only patients in sinus rhythm; the others were in atrial fibrillation. One patient with a negative operative diagnosis of TR had no contrast appearance in his IVC during contrast echocardiography.

M-mode vs Two-dimensional Echocardiography

Thirteen of the study subjects had no IVC contrast by either M-mode or two-dimensional echocardiography despite deep inspiration and the Valsalva maneuver. Thirty-eight had the same contrast pattern diagnosed both by M-mode and two-dimensional echocardiography (27 v-wave synchronous, eight a-wave synchronous and three random patterns). Within this group, timing analysis was considerably simpler from M-mode recordings, which allowed measurement of contrast appearance, and simplified comparison of the ECG, echo and respiratory events. Timing analysis of two-dimensional echoes involved review of videotapes and repeated slow-motion analysis, with tedious loading and unloading of tapes onto the video head for forward and reverse tape motion.

Eleven patients had IVC contrast on their M-mode studies but no definite contrast on their two-dimensional studies. Their M-mode patterns were as follows: four a-wave synchronous, four random and three v-wave synchronous. Only two of these patients, neither of whom had TR, had operative or angiographic study of the tricuspid valve; one had an M-mode a-wave synchronous pattern and the other had a random pattern. Two further normal subjects had small amounts of a-wave synchronous contrast appearance on M-mode but none on two-dimensional echocardiography.

Assessment for a "back-and-forth" pattern of contrast flow across the tricuspid valve on two-dimensional studies was difficult because of the normal slight retrograde motion of contrast in the right
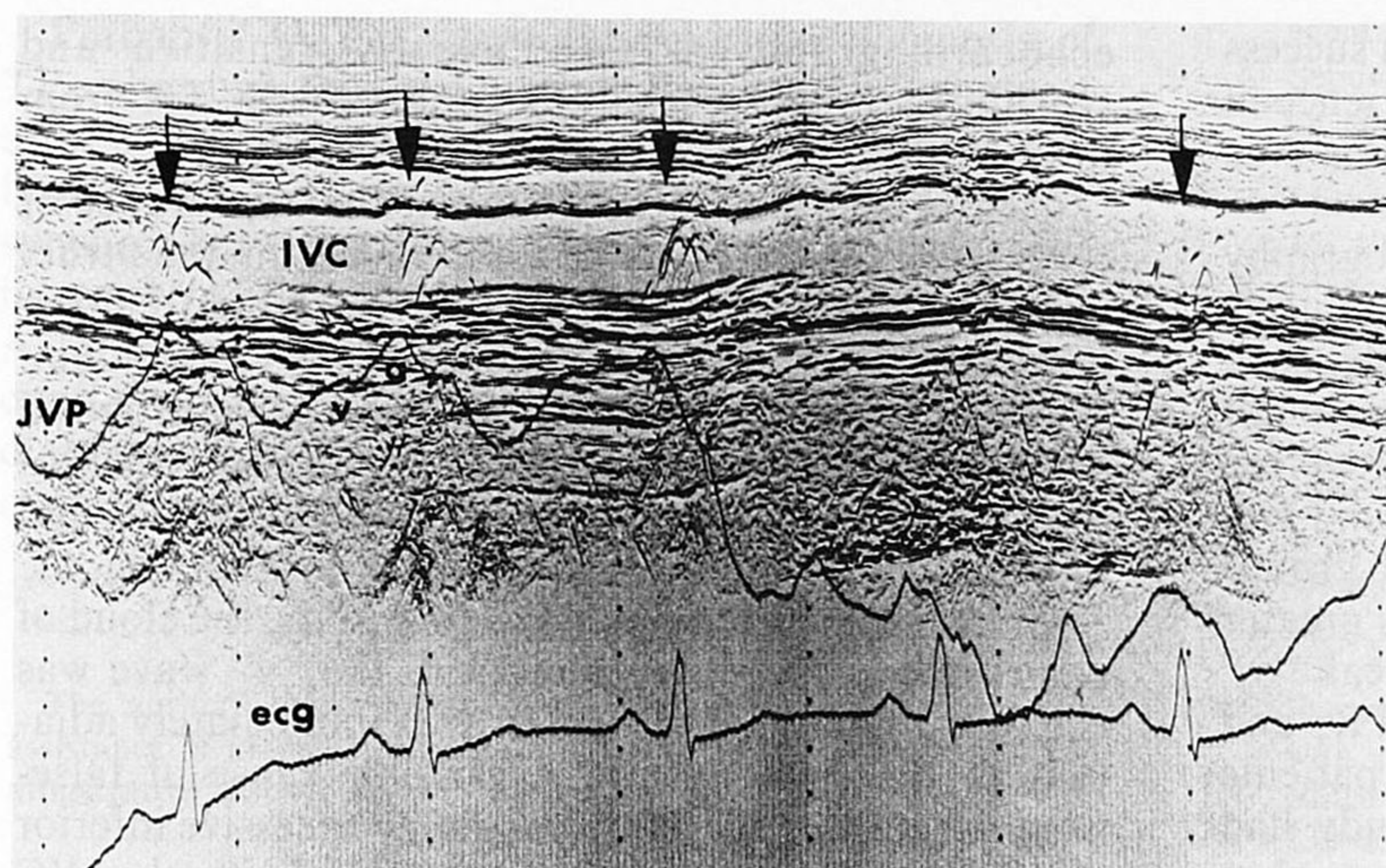
FIGURE 4. *M-mode contrast inferior vena cava (IVC) echocardiogram showing an a-wave synchronous pattern in a patient with pulmonic stenosis and no tricuspid pathology. The jugular venous pulse tracing (JVP) shows a large respiratory variation but always a prominent "a" wave and x' descent, making significant tricuspid regurgitation unlikely. Contrast appears in the IVC (arrows) during the late part of the JVP "a" pulsation, suggesting retrograde flow due to forceful atrial contraction. a = "a" pulsation; v = "v" pulsation.*
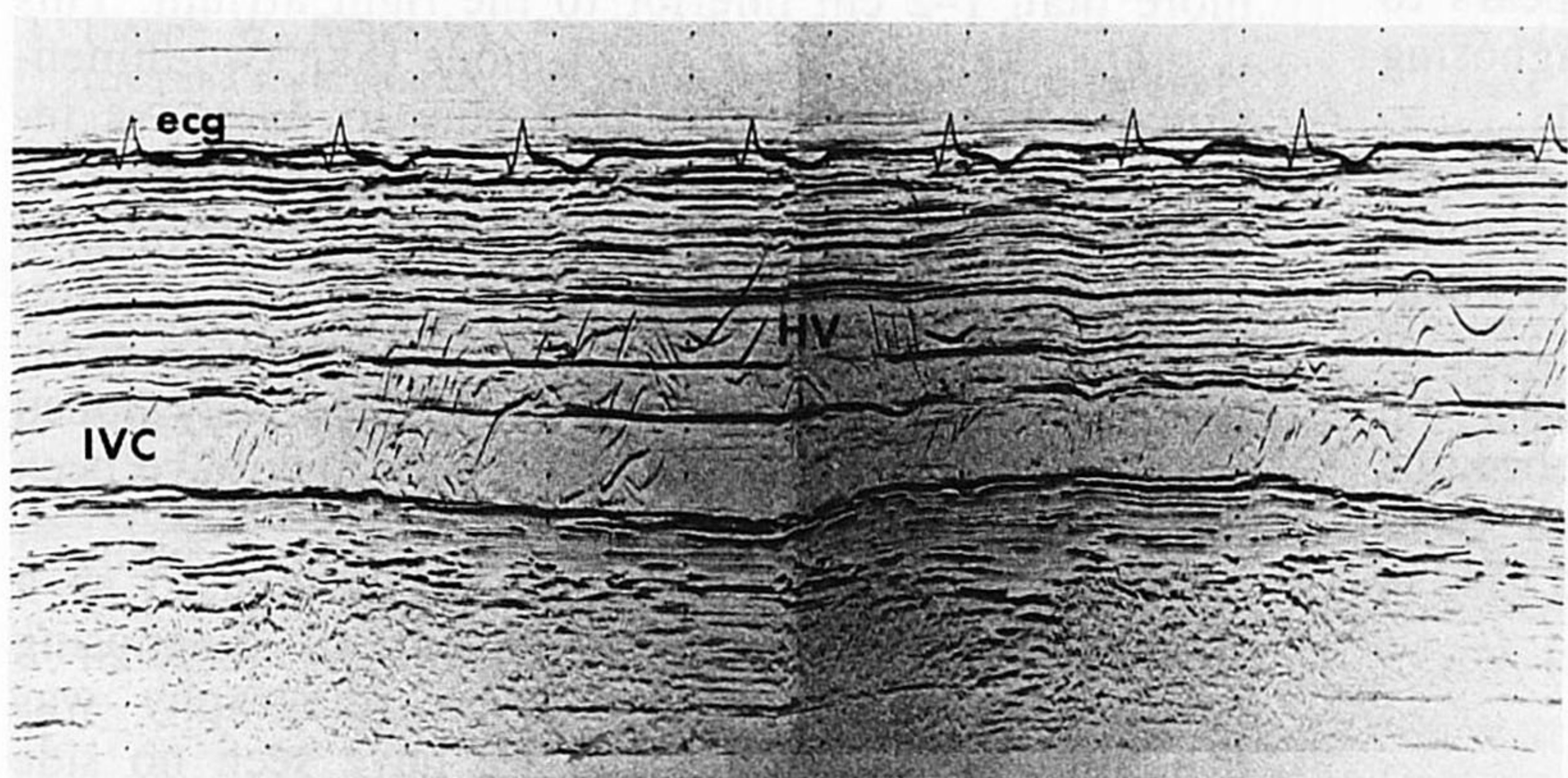

FIGURE 5. *M-mode contrast inferior vena cava (IVC) echocardiogram showing a "random" pattern of contrast appearance in the IVC and hepatic vein (HV), with retrograde flow (upward-sloping contrast lines) occurring with no fixed relation to the cardiac cycle. This is the most common false-positive pattern of contrast appearance in patients with atrial fibrillation.*

ventricle at the time of closing of the tricuspid valve. Only a minority of patients with v-wave synchronous IVC contrast patterns had definite "back-and-forth" motion as assessed subjectively by two observers in the echo lab at the time of the study.

Discussion

Diagnostic Tests for TR

TR may be an obvious diagnosis clinically. In patients with prominent jugular "v" waves, a positive Carvalho sign and a pulsatile liver, further studies are not needed to establish the diagnosis. However, in adults, TR is usually associated with disease of the left side of the heart and pulmonary hypertension, and most patients with TR are in atrial fibrillation.[6, 7] In the absence of sinus rhythm, the jugular venous pulse is less useful in diagnosing TR, and clinical diagnosis is further obscured because many patients with TR also have systolic murmurs of aortic or mitral valve origin. Thus, an accurate diagnostic test for TR would be useful. Right ventricular angiography is not an ideal test because it is invasive and false-positive studies may be caused by catheter interference with normal tricuspid valve mechanics. Unfortunately, there is no accepted "gold standard" for the diagnosis of TR.[8, 9] Even intraoperative right atrial palpation may be subject to false negatives due to insufficiently

widespread palpation, and false-positive palpation of a thrill in the right atrium can result from intraoperative manipulation of the heart with resulting distortion and incompetence of the tricuspid valve. Perhaps one of the two false-negative echo contrast studies in our series was in fact a false-positive palpation due to a transmitted thrill caused by a flail mitral valve leaflet in a patient with a thrill that was also palpated on the thoracic wall. Because the palpated thrill was fairly localized and superior on the right atrium, another possibility is that the regurgitant tricuspid jet was superiorly directed, thereby explaining the failure to visualize contrast in the IVC. However, because there is no better standard than angiocardiography or intraoperative palpation against which to judge the proposed echo contrast technique, it is prudent to consider this case as a false-negative echocardiographic study.

Echocardiographic Diagnosis of TR

A major shortcoming of echocardiography is the less-than-100% success rate in acquiring diagnostic information. Subcostal imaging of the IVC, however, is not hampered by the usual echocardiographic "window" difficulties. In fact, all 62 patients in the current series had successful two-dimensional and M-mode imaging of the IVC. M-mode imaging without initial

two-dimensional study should have a very high success rate after the examiner has gained some experience in IVC echocardiography, though this hypothesis was not tested in the present study.

It would be desirable if IVC echocardiography could separate patients with TR from normal subjects on the basis of an entirely noninvasive variable, such as IVC dimension or systolic pulsation. We could not do this in the present study, because there was overlap in IVC dimension between the two groups, and frequently patients in both the TR and non-TR groups had no detectable pulsations. IVC dimensions greater thn 24 mm (measured at onset of QRS or peak "v" pulsation) were only seen in patients with TR, and dimensions less than 16 mm were seen only in patients without TR. Most of the patients in this study had IVC dimensions between these values. Contrast echocardiography, a minimally invasive test, appears to offer a sensitive and specific method for diagnosing TR, according to our series and other reports.

Doppler echocardiography may offer an entirely noninvasive echocardiographic method for diagnosing TR.[11] Because the microbubbles that cause ultrasonic contrast are easily detected with Doppler techniques,[12] contrast Doppler echocardiography can be considered. Quantification of TR may become possible with improved Doppler or contrast techniques, though it is not possible by the method used in this study.

Improving the Diagnostic Accuracy of Contrast IVC Echocardiography in TR

The various patterns of IVC contrast appearance must be clearly recognized to exclude a-wave synchronous and random studies and thereby improve the specificity of echocardiography in diagnosing TR. Only v-wave synchronous patterns should suggest the diagnosis of TR. Many normal subjects have a-wave synchronous IVC contrast appearance on deep inspiration.

M-mode tracings are superior to two-dimensional echocardiographic video recordings for analysis of the timing of IVC contrast appearance. M-mode was also more sensitive in detecting the appearance of contrast in the IVC. Thus, M-mode rather than two-dimensional echocardiography should be used routinely when searching for TR with IVC contrast echocardiography, except perhaps in patients in whom locating the IVC by M-mode is difficult. In this situation, the improved spatial orientation of two-dimensional echocardiography may facilitate correct IVC localization. Two-dimensional and M-mode echocardiography, however, are complementary techniques and usually can be performed with the same instrument.

A two-dimensional echocardiographic sign that has been proposed for TR, "back-and-forth" motion of contrast across the tricuspid valve, was too subjective in the current study. Because a slight retrograde motion of contrast near the tricuspid valve as it closes is normal, this sign depends on detection of excessive retrograde motion. We found that two-dimensional echocardiography is insufficiently sensitive and specific to reliably separate patients with TR from those without TR on the basis of this sign.

Clearer analysis of the timing of the appearance of contrast in the IVC may be aided by calling the "true-positive" patterns v-wave synchronous and "false-positive" patterns a-wave synchronous or random. These have advantages over the alternative proposal of "presystolic" and "systolic"[10, 13] because much of the IVC "a" wave comes during electrical systole, and the "v" wave is late systolic and early diastolic (fig. 1).

On two-dimensional echocardiography, the cloud of contrast moving retrogradely with the "v" wave was occasionally limited to a small area immediately adjacent to the right atrium. A possible cause of false-negative studies, therefore, would be excessive inferior angulation of the echo transducer, visualizing the IVC more than 1–2 cm inferior to the right atrium. This is more likely to occur by M-mode than two-dimensional echocardiography. One clue to excessive inferior angulation of the echo transducer is appearance of contrast with a negative slope. If contrast is imaged with a v-wave synchronous pattern, TR can be diagnosed regardless of contrast slope. However, a negative study with only a few "lines" of negatively sloped contrast suggests that the transducer may have been directed too inferiorly.

Medically pure (100%) CO_2 has been used as a roentgenologic i.v. contrast agent in diagnosing pericardial effusion before echocardiography was available. It is safe[14, 15] and we have seen no side effects after small amounts of i.v. CO_2 (1–2 ml per injection, in 5 ml D5W) to obtain echo contrast in over 40 patients.[5] Medically pure CO_2 is commercially marketed and should be distinguished from the less pure CO_2 sold in metal cylinders for use in powering various pneumatic devices. CO_2 is useful for adequate echo contrast delivery to the right atrium. In this way the echocardiographer is certain that lack of IVC contrast is due to lack of retrograde flow in the IVC rather than to inability to detect this flow. If contrast is seen in the IVC with D5W, CO_2 is probably unnecessary, as patients with a-wave synchronous, v-wave synchronous or random patterns after D5W alone have always had the same pattern after CO_2 and D5W. However, we have seen several cases in which an initial injection with D5W failed to yield IVC contrast and subsequent injections with CO_2 and D5W gave IVC contrast. Particularly when antecubital veins are difficult to enter and a smaller hand vein is used, contrast delivery to the central circulation may be insufficient with routine injection techniques. If contrast is not readily apparent in the IVC after an injection, the right side of the heart must be checked from the parasternal or apical transducer position to verify whether contrast has been obtained in adequate density. We suggest that no study be considered negative for TR until the echocardiographer is convinced that adequate central contrast has been achieved. This should reduce the number of false-negative studies and thereby improve the diagnostic sensitivity of contrast IVC echocardiology.

Perhaps CO_2 can cause false-positive diagnosis of TR, although this is doubtful. Because IVC contrast after upper extremity injection must reflect retrograde flow in the IVC, its presence combined with v-wave synchronous timing is unlikely when TR is absent. We have seen no false-positive v-wave synchronous studies. A false-positive diagnosis of TR caused by excessive contrast from CO_2 is less likely than a false-negative diagnosis due to inadequate contrast during routine contrast injections.

Acknowledgment

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