ventricular arrhythmias in the late myocardial infarction period. 1. Conduction characteristics in the infarction zone. Circulation **55:** 686, 1977
7. El-Sherif N, Hope RR, Scherlag BJ, Lazzara R: Re-entrant ventricular arrhythmias in the late myocardial infarction period. 2. Patterns of initiation and termination of re-entry. Circulation **55:** 702, 1977
28. Wellens HJJ, Schuilenburg RM, Durrer D: Electrical stimulation of the heart in patients with ventricular tachycardia. Circulation **46:** 216, 1972
29. Wellens HJJ, Düren DR, Lie KI: Observations on mechanisms of ventricular tachycardia in man. Circulation **54:** 237, 1976

Sudden, Unexpected Death in Avid Dieters Using the Liquid-Protein-Modified-Fast Diet

Observations in 17 Patients and the Role of the Prolonged QT Interval

JEFFREY M. ISNER, M.D., HAROLD E. SOURS, M.D., ALLEN L. PARIS, M.D., VICTOR J. FERRANS, M.D., AND WILLIAM C. ROBERTS, M.D.

SUMMARY **Clinical and morphologic findings are described in 17 patients who died suddenly and unexpectedly during or shortly after use of the liquid-protein-modified-fast diet. Of the 17 patients, 16 were women, most were young (average age 37 years), and most lost a massive amount of weight (average 41 kg or 35% of their prediet weight) over a short period of time (average 5 months). Eight had one or more episodes of syncope. Multiple-lead ECGs were recorded in 10 patients. All had normal sinus rhythm; all had episodes of ventricular tachycardia; nine and possibly 10 patients had prolongation of the QT interval, unassociated with the recognized causes of QT interval prolongation in at least seven of the nine patients; and nine had diminished amplitude of the QRS complexes ("low voltage"). Histologic study of left ventricular myocardium in 14 patients disclosed attenuated myocardial fibers in 12, increased lipofuscin pigment in 11, and mononuclear-cell myocarditis in one. Similar histologic findings, however, also were found in 16 cachectic control subjects studied in similar fashion, but ECGs in them showed no prolongation of QT intervals or episodes of ventricular tachycardia. Thus, semistarvation, particularly in the face of antecedent obesity, is a cause of acquired QT interval prolongation, and repeated ECGs are recommended in patients on semistarvation diets for treatment of obesity.**

IN 1976 a book entitled *The Last Chance Diet*[1] was published and almost immediately, several liquid-protein-modified-fast (LPMF) diets became very popular and fashionable as means of rapid weight reduction. These diets were intended to serve as the dieter's only source of calories. Between January 1, 1977 and December 31, 1977, it was estimated that more than 100,000 persons had used one or more of the LPMF diets as their sole source of nourishment for at least 1 month.[2] By August 1977, however, sudden death in several young LPMF diet users was reported to either the Food and Drug Administration (FDA) or the Center for Disease Control (CDC), and between July 1977 and January 1978 at least 60 deaths among avid users of the LPMF diet were reported to the FDA and CDC.[3] In 28 of these 60 patients, there was clinical or necropsy evidence of an underlying disorder that may have contributed to the patient's death, and in 15 other patients information regarding the circumstances of death was incomplete. This report focuses on the other 17 patients who before LPMF dieting were healthy and in whom detailed clinical and/or necropsy information was available. Attention is called to a poorly documented cause of QT interval prolongation and sudden death.

From the Pathology Branch, National Heart, Lung, and Blood Institute, Bethesda, Maryland, and the Center for Disease Control, Atlanta, Georgia.

Address for correspondence: William C. Roberts, M.D., Building 10A, Room 3E30, National Institutes of Health, Bethesda, Maryland 20205.

Received April 2, 1979; revision accepted June 4, 1979.
Circulation 60, No. 6, 1979.

Patients

Certain clinical and morphologic findings in the 17 patients are summarized in table 1. Patients 3 and 5,[4] 8,[5] and 10[6] have been reported by other investigators. Symptoms attributable to cardiac dysfunction were minimal to absent in all 17 patients. None had evidence of congestive cardiac failure. Only four patients (6, 9, 11 and 12) (table 1) had evidence of systemic hypertension at some time. Death was sudden and occurred outside the hospital in six patients. Of the other 11 patients, eight presented with syncope and subsequently died in the hospital; the other three were comatose upon admission to the hospital and each died soon thereafter.

TABLE 1. *Clinical and Morphologic Findings in the 17 Patients on the Liquid-Protein-Modified-Fast Diet*

Pt no.	Age (years) at death	Sex	S	VPC	VT	VF	QTIP	LV*	Months on diet	Height (cm)
1	23	F	0	+	+	+	−	+	4	175
2	25	F	+	0	+	+	−	−	5	167
3	32	F	+	+	+	+	+	+	5	167
4	32	F	+	+	+	+	+	+	6	165
5	33	F	+	+	+	+	+	+	8	162
6	33	F	0	−	+	−	−§	0	4	162
7	33	F	0	−	−	−	−	−	3	162
8	34	F	+	0	+	+	+	+	5	167
9	36	F	0	−	−	−	−	−	7	160
10	38	F	+	+	+	+	+	+	8	173
11	41	F	0	−	−	−	+	+	5	165
12	43	M	0	+	+	+	+	+	7	193
13	44	F	0	−	−	−	−	−	5	165
14	45	F	0	−	−	−	−	−	2	173
15	50	F	0	−	−	−	−	−	2	157
16	51	F	+	+	+	+	+	−	7	173
17¶	44	F	+	+	+	+	+	+	3	160

*Low voltage defined as the sum of QRS in leads I, II and III $\leq$ 1.5 mV.

†Predicted heart weight calculated as 0.004 × body weight.[46, 47]

‡Heart weight lost = $\frac{\text{PHW at start of diet} - \text{actual heart weight at autopsy}}{\text{PHW at start of diet}}$

§QT_o = 0.28 second, QT_e = 0.70 second measured during sinus tachycardia (150 beats/min).

¶Autopsy not performed.

Abbreviations: S = syncope; VPC = ventricular premature complex; VT = ventricular tachycardia; VF = ventricular fibrillation; QTIP = QT-interval prolongation; LV = low voltage; BW = body weight; A = autopsy; PHW = predicted heart weight; AHW = actual heart weight; HW = heart weight; MYO = myocarditis; FC = fatty changes; + = positive; − = information not available.

Electrocardiographic data recorded during the period of dieting was available in 12 patients (fig. 1). In one patient, only a rhythm strip was available, and in a second patient the 12-lead ECG had been recorded during an episode of ventricular tachycardia. Of the other 10 patients, a recording was obtained in eight of them during the week before death, including two in whom the recordings were done after cardiac arrest with successful resuscitation — in one, 8 weeks, and in another 3 weeks before death. In eight patients

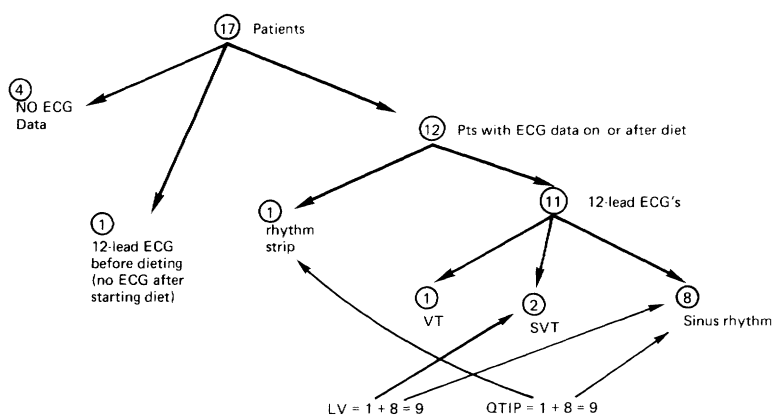

FIGURE 1. *Schematic depiction of timing and extent of electrocardiographic data available among the 17 liquid-protein-modified-fast dieters described in this report. LV = low voltage; PTD = prior to death; QTIP = QT interval prolongation; SVT = supraventricular tachycardia; VT = ventricular tachycardia.*

TABLE 1. (*Continued*)

BW (kg)		PHW (g)†		AHW (g)	BW	HW‡		Liver	
Prior to diet	At A	Prior to diet	At A	At A	lost (%)	lost (%)	MYO	Weight (g)	FC
128	90	512	360	325	30	36	0	—	0
126	63	504	252	305	50	40	+	1750	+
104	68	416	272	300	35	28	0	1600	+
113	64	452	256	260	43	43	0	1650	0
112	71	448	284	300	36	33	0	1870	+
106	73	424	292	260	31	38	0	1600	+
85	59	340	236	—	30	—	0	2000	0
107	66	428	264	300	38	30	0	—	−
135	87	540	348	300	36	44	0	—	0
153	90	612	360	325	41	47	0	1750	0
104	68	416	272	300	35	28	0	1490	0
184	100	736	408	430	46	42	0	1840	0
103	63	412	252	275	39	50	0	1410	0
95	82	380	328	300	14	21	0	—	0
73	54	292	220	310	25	—§	0	1600	0
108	64	432	256	280	41	35	0	1360	+
97	79	388	320	—	18	—	0	—	−

in whom tracings were obtained before cardiac arrest, the rates ranged from 64–88 beats/min (average 75 beats/min). Nine of the 10 patients in a supraventricular rhythm had decreased QRS voltage (table 2, figs. 2 and 3). In four patients in whom both pre- and post-diet ECGs were available, the QRS voltage decreased from 23 to 50% (average 38%) (table 2, fig. 2). The QT interval (measured from the onset of the Q, or in the absence of a Q wave the R wave, to the terminal inscription of the T wave in the lead where the termination of the T wave could be most clearly identified) was unequivocally prolonged in nine patients (figs. 2 and 3); in the tenth patient, the ECG was recorded only during tachycardia, and therefore, accurate determination of the QT interval was not possible (table 2). The observed QT interval ranged from 0.37–0.60 second, while the QT interval corrected for rate by Bazett's formula ($QT_c = QT_o/\sqrt{R\text{-}R}$)[7] varied from 0.45–0.65 second. The QT interval was prolonged both by comparison of the corrected QT interval to the arbitrary upper normal limit of 0.44 second[8] and by comparison of the observed QT interval to the age- and rate-adjusted normal values of Simonson and associates.[9] In four of the nine with unequivocally prolonged QT intervals while dieting, predieting ECGs are available: three had normal and one had a prolonged QT interval. The latter patient had normal hearing and had been asymptomatic before dieting on the LPMF regimen.

Ventricular tachycardia was documented in all 11 patients in whom electrocardiographic data were available[1](see footnote in fig. 1); in eight of these 11 patients a 12-lead ECG was available and in all eight there was prolongation of the QT interval. The QRS complexes in four patients with ventricular tachycardia displayed periodic axis shifts characteristic of the *torsade de pointes* pattern.[10] The episodes of ventricular tachycardia in all 11 patients were often refractory to multiple combinations of medical therapy: lidocaine was ineffective in 10 patients; procainamide was ineffective in five patients; phenytoin sodium was ineffective in four patients; propranolol was ineffective in seven patients. (Quinidine was not used in any patient.) A left stellate ganglion blockade (without an associated Horner's sign) had no effect in one patient. Ventricular overdrive pacing was similarly ineffective in another patient. Serum magnesium and calcium levels, available in nine patients, were normal in nine and eight patients, respectively. Serum potassium levels ranged from 2.2–5.2 mEq/l (table 2); in at least four patients the serum potassium was unequivocally normal within 24 hours of the time of death.

Necropsy in 16 of the 17 patients disclosed no increased amounts of fluid in any of the body cavities in any patient. The weight of the liver (known in 12 patients) ranged from 1360–1900 g (average 1650 g); histologically, fatty change was present in five patients and in them its extent was mild. The brain, bowel, lungs, spleen and kidneys appeared grossly normal in all 16 patients. The weight of the hearts (known in 15 patients) ranged from 260–430 g (average 305 g) and was decreased in proportion to the documented decrease in body weight (i.e., there was no "sparing" of myocardial mass). The myocardium in each patient was devoid, by visual inspection, of foci of fibrosis or necrosis. One patient (no. 12, table 1), however, had a several foci of myocytolysis.[11] The four cardiac valves were normal in all 16 patients. The origin and distribution of the major epicardial cor-

TABLE 2. *Electrocardiographic and Electrolyte Data in the 17 Patients Who Used the Liquid-Protein-Modified Fast Diet*

Pt no.	No. days PTD ECG recorded	Sum of QRS I + II + III ≤ 15 mm	QRS ≤5 mm in each standard lead	Σ QRS I + aV_F + V_1 (mm)		
				Prediet	During diet	% Decrease on diet
1	1	+	+	—	14	—
2	—	—	—	—	—	—
3	3	+	0	—	—	—
4	1	+	0	—	17	—
5	3	+	+	20	10	50
6	1	0	0	35	27	23
7	—	—	—	—	—	—
8	1	+	+	—	15	—
9	—	—	—	—	—	—
10	1	+	+	26	14	46
11	20	+	+	—	14	—
12	1	+	0	27	18	33
13	275	—	—	21	—	—
14	—	—	—	—	—	—
15	—	—	—	—	—	—
16	1	—	—	—	—	—
17	1	+	+	—	10	—

*$QT_c = QT_o \times \sqrt{\text{RR interval}}$ 7

†QT_o = observed QT interval.

‡QT interval measured during sinus tachycardia (150 beats/min); since measurement may be unreliable at this rate, this patient is not included as "documented QTIP" in text.

Abbreviations: PTA = prior to admission; PTD = prior to death; + = positive; — = information not available; Nl = normal.

onary arteries were normal in all 16 patients and all major arteries were free of significant atherosclerotic plaquing.

One to 20 (average six) histologic sections of left ventricular myocardium, extending from endocardium to epicardium, were examined in 14 patients. Although there was considerable variation from patient to patient and from area to area within individual patients, myocardial fiber size was clearly decreased in 12 patients (86%) and lipofuscin pigment was clearly increased in 11 patients (79%) (fig. 4). The five patients who lost > 40% of their body weight had greater myocardial fiber attenuation than did the patients who lost a smaller percentage of their original body weight. The degree of fiber attentuation, however, was not directly proportional to heart weight or duration of dieting. The range of heart weights and duration of dieting, however, was extremely small, and, therefore, differences might not be expected. The extent of the lipofuscin pigment deposition in the 14 study patients did not vary significantly with age, but the oldest patient was only age 51 years.

Inflammatory cells were found in the interstitium of the left ventricular myocardium in three patients. In each, the inflammatory cells consisted of lymphocytes, plasma cells and histiocytes, and occasionally granulocytes, including a rare eosinophil. The amount of interstitial mononuclear cell inflammation was considerable in patient 2 (table 1, fig. 5) and minimal in patients 6 and 12 (table 1). Special stains for bacteria and fungi disclosed no stainable organisms.

Control Subjects

To evaluate the specificity and significance of the myocardial histologic findings in the LPMF dieters, two groups of control subjects were evaluated in similar fashion. Group A, consisted of 16 patients who were severely cachectic at death from nondieting causes. Of the 16 patients, 13 died from malignant neoplasms, and three from chronic central nervous system illnesses associated with severe wasting. No patient had a known history of cardiac disease and none had received medication known to be cardiotoxic. The 16 control subjects ranged in age from 15–70 years (average 51 years); eight were men and eight were women. All 16 either weighed less than 55 kg (average 47 kg) at death or had lost more than 25% of their total body mass (average 29.2%). Compared to the LPMF dieters, the morphologic findings in control group A patients were qualitatively similar in terms of fiber attenuation. The extent of lipofuscin deposits was greater among patients in control group A than in users of the LPMF, but their average age was older. Four group A patients had sparse focal aggregations of inflammatory cells, but in none were

TABLE 2. (*Continued*)

Prediet QT_c (sec)	QT interval on diet			QRS Interval (sec)	K^+ (mEq/l) on adm. (range PTA)
	QT_c† (sec)	QT_c* (sec)	UNL per Simonson[9]		
—	—	—	—	—	3.9 (3.5–4.9)
—	—	—	—	—	3.0 —
—	0.40	0.46	0.39	0.06	2.9 —
—	0.48	0.55	0.39	0.08	2.8 (3.3–5.1)
0.42	0.44	0.46	0.39	0.08	3.6 (3.6–5.2)
0.38	0.28	0.70‡	—	0.08	3.1 (3.0–4.2)
—	—	—	—	—	—
—	0.54	0.60	0.39	0.08	3.6 (3.1–3.9)
—	—	—	—	—	— (2.2)
0.52	0.48	0.55	0.39	0.08	4.3 (3.8–4.1)
—	0.60	0.59	0.41	0.08	Nl
0.39	0.50	0.52	0.41	0.08	3.2 (3.2–4.3)
0.44	—	—	—	—	— (3.4–4.1)
—	—	—	—	—	— —
—	—	—	—	—	— —
—	0.38	0.49	0.37	0.08	3.8 (3.9–4.2)
—	0.52	0.65	0.37	0.10	3.3 (4.2–4.8)

these extensive enough to warrant the diagnosis of myocarditis.

Electrocardiograms were available in nine patients from control group A (nondieting cachexia) and none had prolonged QT intervals. Two of the nine patients fulfilled criteria for "low voltage," and in a third patient there had been a 28% decrease in the summated QRS voltage of I, aV_F and V_1 over a period of 6 months before death.

The second control group, hereafter called group B, consisted of 15 subjects initially examined by the medical examiner of the District of Columbia because of sudden traumatic (noncardiac) death. No subject had gross evidence of cardiac disease, and none had been on any type of weight-reduction regimen. The 15 subjects ranged in age from 22–67 years (average 44 years); 13 were men and two were women. All 15 were at normal or above normal body weight. With one exception, no attenuation of myocardial fiber size was observed but lipofuscin deposits were similar in extent to those in the users of the LPMF diet. Three patients had minute foci of interstitial myocardial inflammatory cells, but in none were they extensive enough to warrant a diagnosis of myocarditis.

Discussion

The 17 patients described above all died relatively suddenly at relatively young ages (average age 37 years); all had used a LPMF diet as their sole source of calories for several months (average 5 months) because of previous severe obesity (average weight 114 kg); all lost large (average 41 kg or 35% of their immediate predieting body weight) quantities of weight rapidly (average 5 months); at least nine developed fatal ventricular arrhythmias with prolonged QT intervals; and at necropsy most had relatively small hearts, attenuated and pigmented (lipofuscin) ventricular myocardial fibers, and normal or virtually normal noncardiac body organs. Before the onset of dieting, none had had a previous illness of significance and none at any time had received a cardiotoxic drug.

The opportunity to examine a relatively large number (in this report 17) of necropsy patients who were avid users of the LPMF diet clearly indicates that myocarditis, reported previously in several patients on the LPMF diet,[2] is an infrequent finding in these patients. Only one of our 16 necropsy patients had unequivocal histologic evidence of myocarditis and it was of a mononuclear cell variety. Two other patients had a probable increase in interstitial myocardial mononuclear cells, but the number of cells was simply too few to justify a diagnosis of myocarditis. Although sparse foci of lymphocytes have been observed in atrophied hearts,[12] mononuclear cell myocarditis has not been described in persons who died during prolonged periods of starvation or semistarvation.

In contrast, the thinned and pigmented (lipofuscin) myocardial fibers of the left ventricle in our patients are recognized consequences of starvation and have been mentioned previously by others.[13] Likewise, the finding of low voltage among nine of the LPMF dieters is consistent with observations of other patients subjected to severe caloric restriction[14-21] and is presumably related to thinning of the electricity-generating myocardial fibers. There was no evidence in the present group of patients of pericardial effusion,

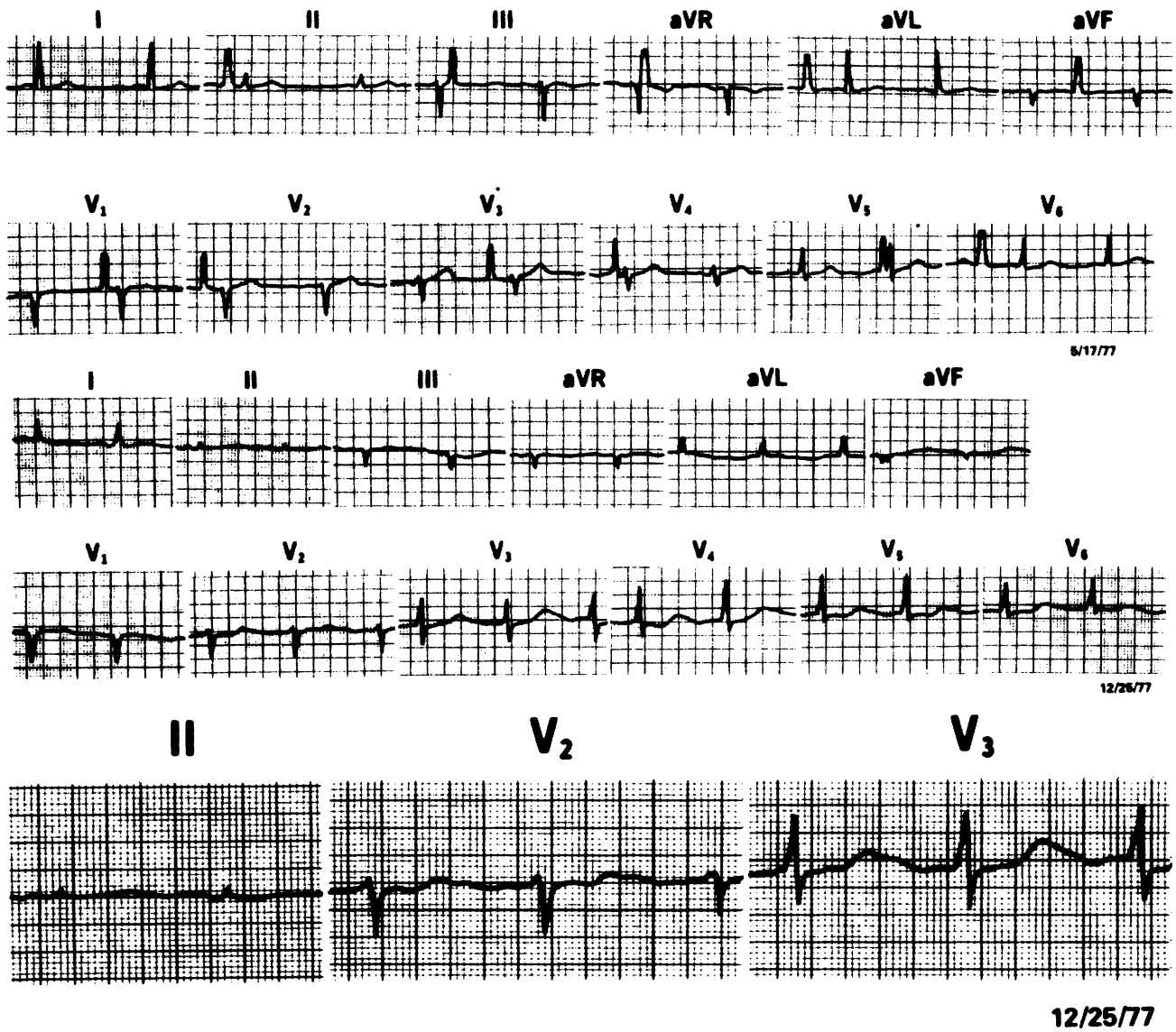

FIGURE 2. *ECG of patient 12, who died on 12/26/77. ECG recorded 1 day earlier (12/25/77) shows a striking reduction in QRS voltage in all three standard leads compared to the predieting ECG recorded on 5/17/77. Close-up of leads II, V_2 and V_3 from the ECG recorded 12/25/77 shows a prolonged QT interval. In leads V_2 and V_3 there is a distinct separation of the T wave from the U wave, allowing measurement of the true QT interval, which in this case measures 0.50 second. The ECGs have been redrawn for clarity; calibration signal artifact is present in leads II, III, aV_R, aVL, aV_F and V_1-V_6 of tracing recorded on 5/17/77.*

myxedema, cardiac amyloidosis or alternative etiologies for the decreased electrical activity of the heart.

The unique feature about these 17 patients is, of course, the fact that most died from ventricular arrhythmias associated with QT-interval prolongation after massive, rapid weight loss while on a LPMF diet. It is reasonable to believe that QT interval prolongation is the underlying cause of the fatal ventricular arrhythmias in these patients, but the cause of the QT prolongation is less clear. The recognized causes of QT-interval prolongation provide potential explanations in at most only two of our 17 patients. A congenital origin is a possible cause of the QT-interval prolongation in our patient 10, who was found to have this electrical abnormality at age 34 years, 4 years before death. Although a possible explanation for the QT-interval prolongation in this patient, a congenital origin of QT prolongation appears to be an unlikely explanation in the other patients: three (patients 5, 6 and 12) had unequivocally normal QT intervals documented before dieting, none were deaf (ruling out the syndrome of congenital QT-interval prolongation associated with deafness[22]), and the infrequent finding in the general population of the syndrome of congenital QT-interval prolongation unassociated with

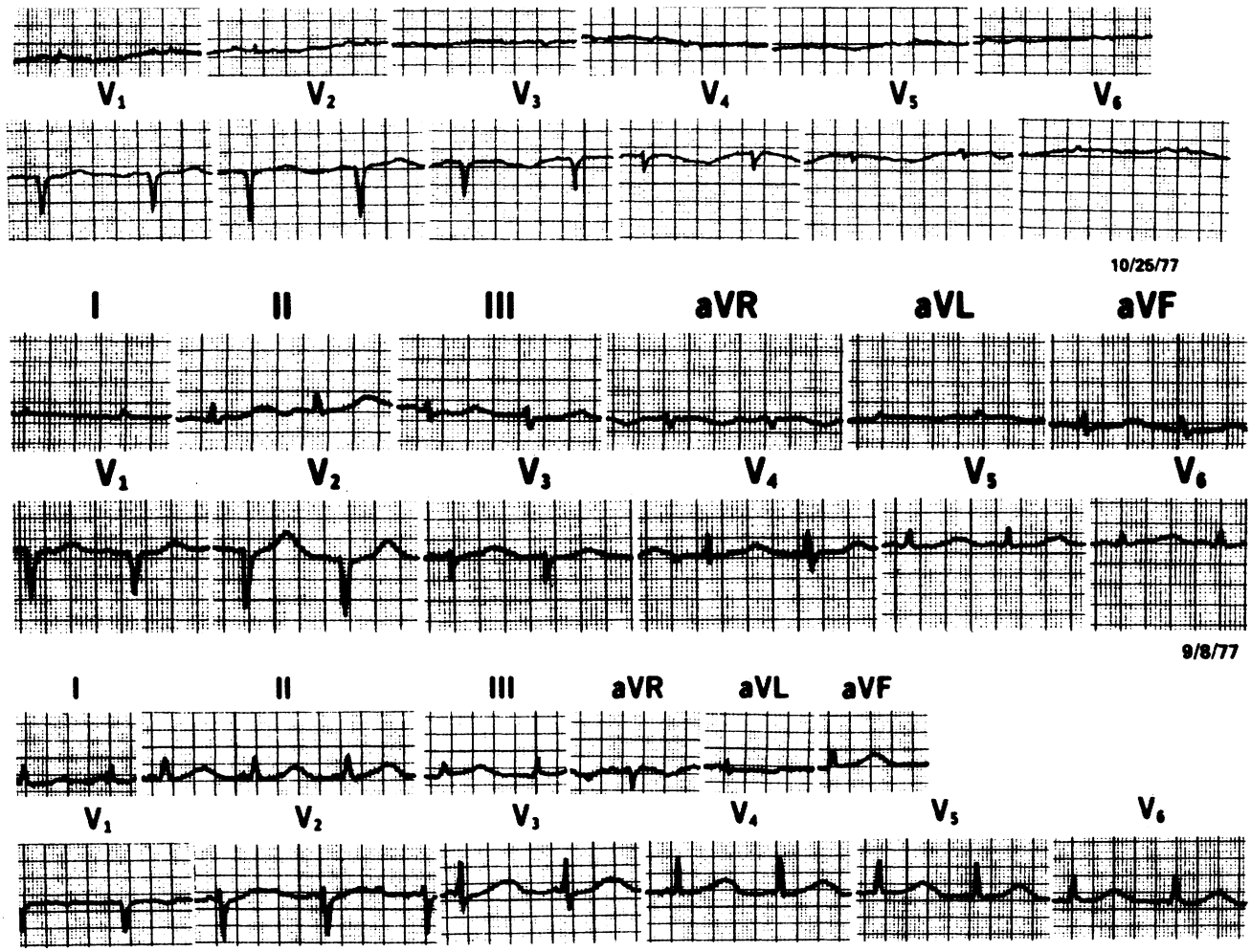

FIGURE 3. *ECGs demonstrating low voltage in each of three patients: patient 5, top; patient 8, center; and patient 11, bottom. All tracings were redrawn for clarity.*

deafness[23, 24] suggests that the observed association would have been unlikely to occur by chance alone.

Hypocalcemia, another recognized cause of QT prolongation, was a possible etiologic factor in only one (no. 17) of our patients. In this patient, however, the serum calcium level was only mildly depressed (7.8 mg/dl), the serum albumin was unknown, and, furthermore, the blood on which the test was performed was drawn shortly after cardiac arrest with successful resuscitation. Thus, hypocalcemia is an inadequate explanation for the QT prolongation in our patients. Hypomagnesemia, another recognized cause of QT prolongation, was not present in any of our nine patients in whom the serum magnesium level was determined. Certain drugs also are recognized to cause QT prolongation. These include quinidine, phenothiazines and possibly phenothiazine derivatives, but none of our patients who had ECGs had received any of these drugs at any time. Thus, this mechanism for QT prolongation can also be excluded in our patients.

Although frequently mentioned as a possible cause, hypokalemia actually is an unproven cause of QT prolongation[25] and, furthermore, it appeared relatively unimportant in our patients. The serum potassium level near death in four of our patients was normal (3.6–4.1 mEq/l) and in four others it was only slightly depressed (2.8–3.3 mEq/l). Hypokalemia alone has never been adequately documented to cause QT-interval prolongation or fatal ventricular tachyarrhythmias. In reported patients with hypokalemia and prolonged QT intervals, a prolonged QT interval generally resulted from the superimposition of a hypokalemic U wave upon the T wave. This finding was interpreted as the QT interval when in fact it was the QU interval.[25-27]

Because the prolonged QT intervals in our patients cannot reasonably be attributed to a congenital origin, hypocalcemia, hypomagnesemia, drugs or hypokalemia, other explanations must be sought. The possibility that the liquid protein products contained toxins is unlikely. Extensive analysis of several com-

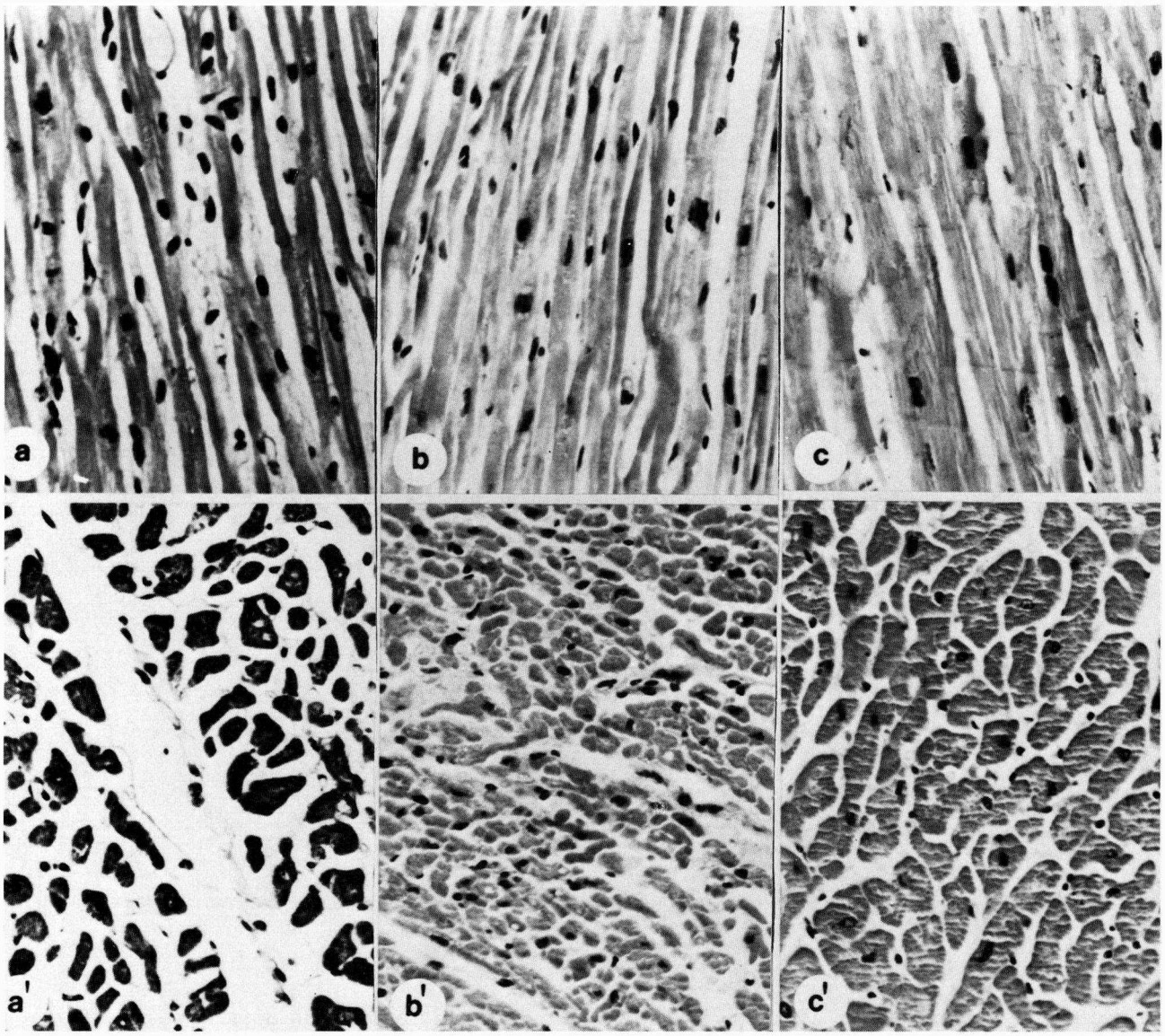

FIGURE 4. *Photomicrographs all at the same magnification (× 330) of portions of left ventricular wall in patient 6 on the liquid-protein-modified-fast diet (a and a'), control cachectic subject (group A, b and b') and control sudden death from trauma subject (group B, c and c'). The upper panels are longitudinal views, and the lower panels, cross-sectional views of the myocardial fibers. The size of the myocardial fibers illustrated in a and b are similar; those in c are much larger. Hematoxylin and eosin stains were used.*

mercial liquid protein preparations disclosed no contamination with dioxins, organohalogens, or organophosphorous compounds, and the content of heavy metals was reported to be below hazardous levels.[28]

Because starvation elevates circulating free fatty acids and because free fatty acids have been shown to be arrhythmogenic in ischemic animal myocardium,[29] the possibility that arrhythmias in our patients resulted from elevated serum levels of free fatty acids has been considered. It is unlikely, however, that they precipitated the ventricular arrhythmias seen in our patients for three reasons. Experimental production of such arrhythmias requires a level of free fatty acids several times in excess of that which occurs in the starving human, in whom the elevation of circulating free fatty acids remains limited to one and one-half times normal.[30] Furthermore, there is no evidence that an ischemic substrate was present in our patients, at least before their initial arrhythmia. Finally, this would leave unexplained the associated QT-interval prolongation.

Studies of other persons subjected to starvation or semistarvation, with[20, 31-36] or without[14-19, 21, 37-39] antecedent obesity, have occasionally alluded to but infrequently confirmed the finding of QT-interval prolongation in such subjects (table 3). An exceptional case with clear documentation of QT-interval prolongation unexplained by recognized causes of this phenomenon and unexplained by spurious QT prolongation from superimposition of a U wave on the T wave was

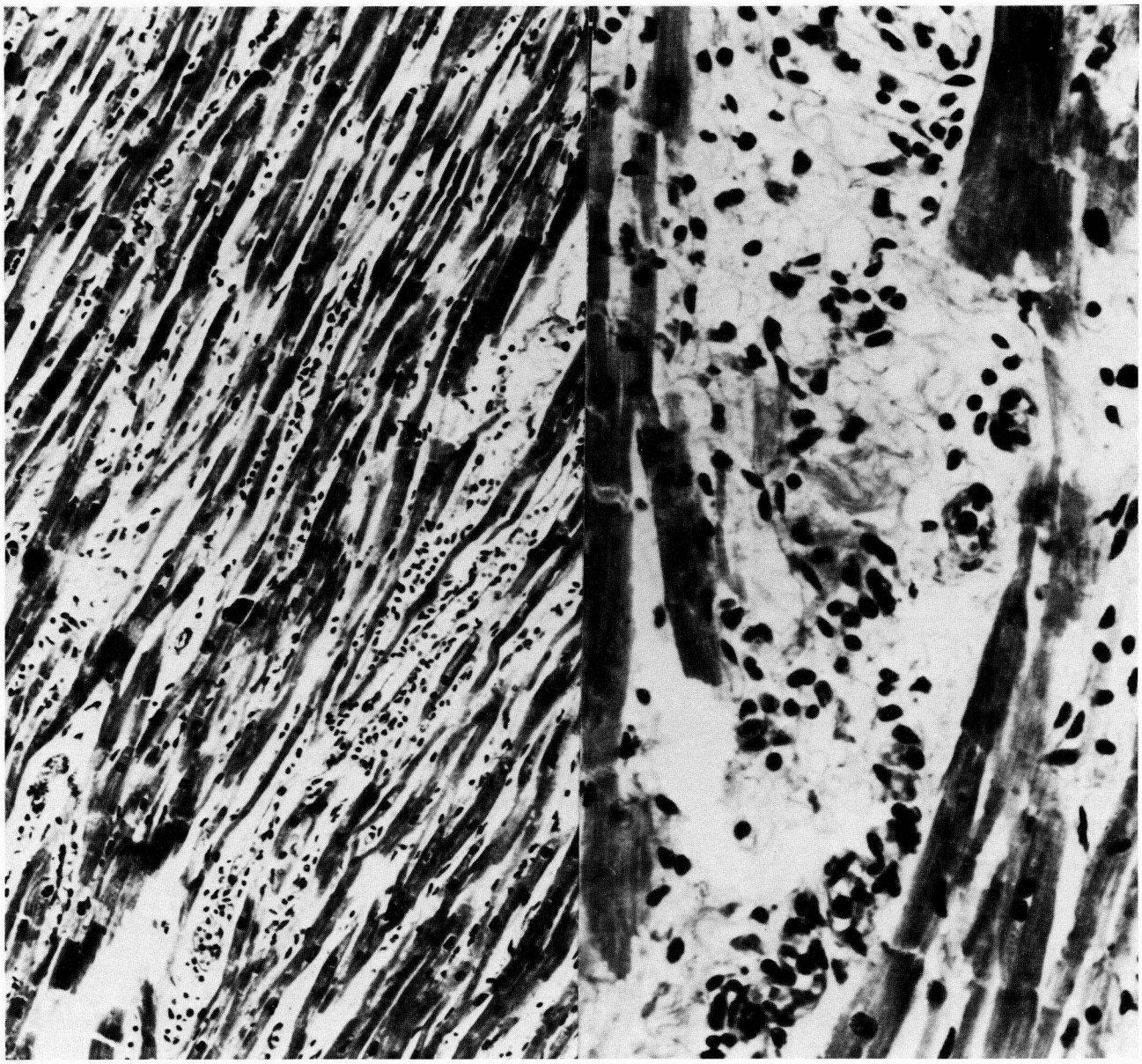

FIGURE 5. *Photomicrographs of myocardium in patient 2, the only one with definite myocarditis. Low-power (× 130) view (left) and high-power (× 880) view (right) showing extensive mononuclear cell infiltrate. Hematoxylin and eosin stains were used.*

reported by Garnett and associates in 1969[20] (table 3). This patient, a woman, died suddenly at age 20 years from a documented ventricular arrhythmia; she had lost 58 kg during 7.5 months on a diet that consisted of unrestricted acaloric salt-free fluids, folic acid, vitamins A, B, D and sporadic amino acid supplements. This diet was similar to the LPMF diets used by our patients, although the caloric value of Garnett's diet was lower than that of the LPMF dieters.

The lack of electrocardiographic data available in most of the remaining studies describing various effects of starvation and semistarvation (table 3) makes it difficult to estimate the true frequency of QT interval prolongation among patients subjected to severe caloric restriction. Patients in some of these other studies may have had QT-interval prolongation that was asymptomatic at the time caloric restriction was discontinued (as was the case in patients 7, 11, and 12 in the present study) and as a result an ECG was not done and the QT-interval prolongation was missed. Furthermore, a lack of details regarding the extent and rapidity of weight loss among patients in most of these other studies makes it difficult to extrapolate how unique or critical these factors were to the 17 patients in the present study. The 17 LPMF dieters who died were recognized as some of the most fanatic adherents to the diet among their respective clinics and their massive and precipitous weight loss confirms their reputation. However, a substantial

TABLE 3. *Previous Reports of Persons Subjected to Severe Caloric Restriction*

First author (year)	Ref. no.	No. pts	Age (years) Range (average)	No. (%) female	Patients studied	Obesity*	S	SD	Mean† BW (kg)	Mean BW (%) lost
Feil (1936)	14	38	15–76 (41)	17 (45)	Pellagra	—	–	–	—	—
Weiss (1937)	15	120	24–67 (—)	22 (18)	Beriberi	—	5	–	—	—
Apfelbaum (1946)	16	18	16–30 (—)	—	War, famine	—	–	–	29	—
Cardozo (1946)	17	29	27–74 (55)	0	War, famine	—	–	–	59	—
Ellis (1946)	37	4	23–29 (25)	0	War, famine	0	–	–	—	—
Simonson (1946)	18	32	20–33 (26)	0	Nl	0	0	0	61	24
Smythe (1962)	19	98	—	—	Kwashiorkor	—	–	–	—	—
Drenick (1964)	31	11	33–71 (48)	10 (90)	Obesity	+	–	0	—	—
Spencer (1968)	32	12	29–75 (57)	8 (67)	Obesity	+	0	2	100	12
Garnett (1969)	20	1	20	1 (100)	Obesity	+	1	1	60	50
Thurston (1974)	38	9	13–18 (16)	1 (11)	AN	—	–	0	—	>10
Kempner (1975)	33	106	17–65 (34)	59 (56)	Obesity	+	0	0	80	44
Vertes (1977)	34–35	519	16–72 (40)	405 (78)	Obesity	+	0	4	—	—**
Bistrian (1978)	36	800	—	—	Obesity	+	–	0	—	—††
Heymsfield (1978)	39	10	34–76 (49)	7 (70)	Cachexia	—	0	0	43	≥25
Gottdiener (1978)	21	11	12–32 (22)	11 (100)	AN	—	0	0	30	>25

*Immediately preceding period of caloric restriction.
†Body weight at end of caloric restriction.
‡"Several."
§Mean decrease in QRS amplitude = 9 mm.
¶One to 2 kg/wk.
**One to 3 kg/wk.
††Three patients showed a mean increase of 29% in QRS amplitude after refeeding.
Abbreviations: S = syncope; SD = sudden death; BW = body weight; VT = ventricular tachycardia; VF = ventricular fibrillation; LV = low voltage; QTIP = QT-interval prolongation; Nl = normal; AN = anorexia nervosa; + = positive; — = information not available.

number of patients have lost similar amounts of weight over similar periods of time without having died (table 3). Thus, it is difficult to draw conclusions at this time as to whether the massive and precipitous weight loss in our 17 patients was the primary factor underlying their electrocardiographic abnormalities and sudden death.

An intriguing possibility that might explain both the arrhythmias and the underlying QT-interval prolongation is that the rapidity and extent of weight loss that these dieters experienced induced undefined metabolic alterations affecting primarily the central nervous system, and secondarily, the electrical system of the heart. There is extensive evidence that starvation induces pathologic alterations of the hypothalamic-pituitary axis of the central nervous system.[30] Information supporting a critical role for the nervous system in the genesis of cardiac arrhythmias,[40] including those related to QT-interval prolongation,[8, 41-45] might provide the link between starvation/semistarvation and secondary electrocardiographic changes.

The pathogenesis of QT-interval prolongation in the LPMF dieters thus remains enigmatic. Its identification, however, may provide not only the key to the mechanism of QT-interval prolongation in our dieting patients, but, more important, in patients with QT-interval prolongation of both the idiopathic and acquired types. Finally, serial electrocardiographic monitoring, although not failsafe, should be the single most important aspect of medical supervision in patients subjected to semistarvation for the treatment of morbid obesity.

Acknowledgment

The assistance of Drs. Alan Forbes and Victor Frattali of the Food and Drug Administration in the completion of this project is gratefully acknowledged.

References

1. Linn R, Stuart SL: The Last Chance Diet. Secaucus NJ, Lyle Stuart Inc, 1976
2. Schucker RE, Gunn WJ: A national survey of the use of protein products in conjunction with weight reduction diets among American women. Atlanta, Center for Disease Control, 1978, p 73
3. Gregg MB (ed): Deaths associated with liquid protein diets. Morbidity Mortality Weekly Rep **26:** 383, 1977
4. Singh BN, Gaarder TD, Kanegae T, Goldstein M, Montgomerie JZ, Mills H: Liquid protein diets and *torsade de pointes*. JAMA **240:** 115, 1978
5. Brown JM, Yetter JF, Spicer MJ, Jones JD: Cardiac complications of protein-sparing modified fasting. JAMA **240:** 120, 1978
6. Michiel RR, Sneider JS, Dickstein RA, Hagman HH, Eich RH: Sudden death in a patient on a liquid protein diet. N Engl J Med **298:** 1005, 1978

TABLE 3. *(Continued)*

Time (mos) on diet	Pts with ECG	VT or VF	LV	Alleged QTIP	QT corrected for Rate	QT corrected for Age	U wave excluded	QRS Nl	Electrolytes Nl K^+	Electrolytes Nl Ca^{++}	Electrolytes Nl Mg^{++}
—	38	—	1	7	+	0	—	+	—	—	—
—	67	—	6	30	+	0	—	—	—	—	—
—	12	—	18	—	—	—	—	—	—	—	—
—	15	—	+‡	4	+	+	—	0	—	—	—
4	4	0	0	4	+	+	0	0	—	+	—
6	32	0	+§	0	+	+	+	+	+	+	—
—	98	—	49	47	+	0	0	—	—	—	—
<4	0	0	—	0	—	—	—	—	—	—	—
<2	12	1	—	0	—	—	—	0	+	+	—
7	1	1	1	1	+	+	+	+	+	+	+
≥3	9	0	—	5	0	0	—	—	+	—	—
9	—	0	—	0	—	—	—	—	—	—	—
≤23	—	—	—	0	—	—	—	—	—	—	—
—	—	—	—	0	—	—	—	—	—	—	—
24	10	0	0	0	—	—	—	+	+	+	+
—	11	1	+§§	0	+	+	—	+	+	+	+

7. Bazett HC: An analysis of the time-relations of electrocardiograms. Heart **7:** 353, 1920
8. Moss AJ, Schwartz PJ: Sudden death and the idiopathic long Q-T syndrome. Am J Med **66:** 6, 1979
9. Simonson E, Cady LD, Woodbury M: The normal Q-T interval. Am Heart J **63:** 747, 1962
10. Krikler DM, Curry PVL: *Torsade de pointes,* an atypical ventricular tachycardia. Br Heart J **38:** 117, 1976
11. Ferrans VJ, Buja LM, Maron BJ: Myofibrillar abnormalities following cardiac muscle injury. *In* Pathophysiology and Morphology of Myocardial Cell Alteration, vol 6. Recent Advances in Studies on Cardiac Structure and Metabolism, edited by Fleckenstein A. Baltimore, University Park Press, 1975, p 371
12. Stein J, Fenigstein H: Anatomie pathologique de la maladie de famine. *In* Maladie de Famine. Recherches Cliniques sur la Famine Executées dans le Ghetto de Varsovie en 1942, edited by Apfelbaum E. Am Joint Distribution Committee, Warsaw, 1946, p 21
13. Keys A, Brožek J, Henschel A, Mickelsen O, Taylor HL: The Biology of Human Starvation. Minneapolis, University of Minnesota Press, 1950, p 206
14. Feil H: A clinical study of the electrocardiogram and of the phases of cardiac systole in pellagra. Am Heart J **11:** 173, 1936
15. Weiss S, Wilkins RW: The nature of the cardiovascular disturbances in nutritional deficiency states (beriberi). Ann Intern Med **11:** 104, 1937
16. Apfelbaum-Kowalski E, Pakszwer R, Zarchi J, Heller A, Askanas Z: Recherches cliniques sur la pathologie du système circulatoire dans la cachexie du famine, *In* Maladie de Famine. Recherches Cliniques Sur la Famine Executées dans le Ghetto de Varsovie en 1942, edited by Apfelbaum E. Am Joint Distribution Committee, Warsaw, 1946, p 189
17. Cardozo El, Eggink P: Circulation failure in hunger edema. Can Med Assoc J **54:** 145, 1946
18. Simonson E, Henschel A, Keys A: The electrocardiogram of man in semistarvation and subsequent rehabilitation. Am Heart J **35:** 584, 1948
19. Smythe PM, Swanepoel A, Campbell JAH: The heart in kwashiorkor. Br Heart J **1:** 67, 1962
20. Garnett ES, Ford J, Barnard DL, Goodbody RA, Woodehouse MA: Gross fragmentation of cardiac myofibrils after therapeutic starvation for obesity. Lancet **1:** 914, 1969
21. Gottdiener JS, Gross HA, Henry WL, Borer JS, Ebert MH: Effects of self-induced starvation on cardiac size and function in anorexia nervosa. Circulation **58:** 425, 1978
22. Jervell A, Lange-Nielsen F: Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval, and sudden death. Am Heart J **54:** 59, 1957
23. Romano C, Gemme G, Pongiglione R: Aritimie cardiache rare dell'eta pediatrica. Clin Pediatr (Bologna) **45:** 656, 1963
24. Ward O: A new familial cardiac syndrome in children. JAMA **54:** 103, 1964
25. Surawicz B, Lepeschkin E: The electrocardiographic pattern of hypopotassemia with and without hypocalcemia. Circulation **8:** 801, 1953
26. Surawicz B, Braun HA, Crum WB, Kemp R, Wagner S, Bellet S: Quantitative analysis of the electrocardiographic pattern of hypopotassemia. Circulation **16:** 750, 1957
27. Fisch C, Knoebel SB, Feigenbaum H, Greenspan K: Potassium and the monophasic action potential, electrocardiogram, conduction and arrhythmias. Prog Cardiovasc Dis **8:** 387, 1966
28. FDAers Report on Analyses of Liquid Protein Products. Food Chem News **20:** 11, 1978
29. Sobel BE, Corr PB, Robison AK, Goldstein RA, Witkowski FX, Klein MS: Accumulation of lysophosphoglycerides with arrhythmogenic properties in ischemic myocardium. J Clin Invest **62:** 546, 1978
30. Cahill GF: Starvation in man. N Engl J Med **282:** 668, 1970
31. Drenick EJ, Swendseid ME, Blahd WH, Tuttle SG: Prolonged starvation as treatment for severe obesity. JAMA **187:** 100, 1964
32. Spencer IOB: Death during therapeutic starvation for obesity. Lancet **1:** 1288, 1968
33. Kempner W, Newborg BC, Peschel RL, Skyler JS: Treatment of massive obesity with rice/reduction diet program. An analysis of 106 patients with at least a 45-kg weight loss. Arch Intern Med **135:** 1575, 1975
34. Vertes V, Genuth SM, Hazelton IM: Supplemented fasting as a large-scale out-patient program. JAMA **238:** 2151, 1977
35. Vertes V, Genuth SM, Hazelton IM: Precautions with supplemented fasting. JAMA **238:** 2142, 1978
36. Bistrian BR: Clinical use of a protein-sparing modified fast. JAMA **240:** 2299, 1978
37. Ellis LB: Electrocardiographic abnormalities in severe malnutrition. Br Heart J **8:** 53, 1946

38. Thurston J, Marks P: Electrocardiographic abnormalities in patients with anorexia nervosa. Br Heart J **36:** 719, 1974
39. Heymsfield SB, Bethel RA, Ansley JD, Gibbs DM, Felner JM, Nutter DO: Cardiac abnormalities in cachectic patients before and during nutritional repletion. Am Heart J **95:** 584, 1978
40. Lown B, Verrier RL: Neural activity and ventricular fibrillation. N Engl J Med **294:** 1165, 1976
41. Vincent GM, Abildskov JA, Burgess MJ: Q-T interval syndromes. Prog Cardiovasc Dis **16:** 523, 1974
42. Abildskov JA: Adrenergic effects on the Q-T interval of the electrocardiogram. Am Heart J **92:** 210, 1976
43. Hersch C: Electrocardiographic changes in head injuries. Circulation **23:** 853, 1961
44. Eisalo A, Perasalo J, Halonen PI: Electrocardiographic abnormalities and some laboratory findings in patients with subarachnoid hemorrhage. Br Heart J **34:** 217, 1970
45. Anderson GJ, Woodburn R, Fisch C: Cerebrovascular accident with unusual electrocardiographic changes. Am Heart J **86:** 395, 1973
46. Smith HL: Relation of the weight of the heart to the weight of the body and of the weight of the heart to age. Am Heart J **4:** 79, 1928
47. Amad KH, Brennan JC, Alexander JK: The cardiac pathology of chronic exogenous obesity. Circulation **32:** 740, 1965

The Clinical Value of the Calibrated Apical A Wave and its Relationship to the Fourth Heart Sound

BOUDEWIJN DENEF, M.D., HILAIRE DE GEEST, M.D., AND HUGO KESTELOOT, M.D.

SUMMARY **The amplitude of the calibrated apical A wave (A), its first derivative (dA/dt), its normalized first derivative ([dA/dt]/A) and its value expressed as a percentage of the total systolic deflection (A/H) were derived from calibrated left apexcardiograms in 64 normal subjects and in 150 patients with heart disease. A is significantly increased in patients with pressure and volume overload of the left ventricle, in idiopathic hypertrophic subaortic stenosis, in congestive cardiomyopathy and in ischemic heart disease in the presence of left ventricular asynergy ($p < 0.001$). In aortic stenosis, A is more sensitive to changes in left ventricular compliance than the A/H ratio. Highly significant correlations exist between A and peak dA/dt in normals ($r = 0.98$) and in patients with heart disease ($r = 0.81$–0.99); at an identical A, patients with a dilated left ventricle have lower values for peak dA/dt and a lower index (peak dA/dt)/A ($p < 0.001$). As a result, A and peak dA/dt are considered to be primarily determined by the resistance to ventricular filling during atrial systole. In the presence of a fourth heart sound (S_4), A and peak dA/dt were significantly increased ($p < 0.001$). A peak dA/dt value > 6X/sec is always associated with an S_4. To a certain degree peak dA/dt can differentiate between a physiologic and pathologic S_4. The intensity of S_4 depends more on the rate of rise of the A wave than on its total amplitude.**

THE LEFT APEXCARDIOGRAM (LAC) is widely used to record low-frequency precordial vibrations over the left precordium, and its value in assessing the mechanical behavior of the left ventricle has been repeatedly emphasized.[1-14] The A wave of the LAC reflects the late diastolic response of the left ventricle to atrial systole. The height of the A wave expressed as a percentage of the total systolic deflection of the LAC has been proposed as an index for the noninvasive assessment of left ventricular end-diastolic pressure[15, 16] and left ventricular end-diastolic compliance.[17] An abnormal increase of the A-wave ratio has been found in several types of heart disease,[18-20] but some patients did not have large A waves despite severe heart disease, and normal A-wave ratios have been reported in patients with critical aortic stenosis.[21] A relationship between the height of the apical A wave and the presence of a fourth heart sound (S_4) has also been shown.[17, 21] Some patients with a definite S_4 however, do not have an abnormal A-wave ratio,[21] and the reason for this remains unexplained. Using calibrated apexcardiography and a previously described method,[22] we attempted to clarify these problems and investigate the clinical value of A-wave calibration and its relation to S_4.

Materials and Methods

Calibrated left apexcardiogram tracings (QLACs) were obtained in 25 normal young subjects (mean age 25 ± 4 years), in 39 normal middle-aged subjects (mean age 42 ± 9 years) and in 150 patients with heart disease (mean age 50 ± 12 years). The presence or absence of an S_4 was established prospectively in 103 subjects by means of phonocardiography. In the normal groups, the absence of heart disease was based on cardiac catheterization and coronary arteriography in 14 subjects and on clinical evidence in the remainder (i.e., no previous history of heart disease, normal

From the Department of Cardiology, Sint-Raphael University Clinic, Leuven, Belgium.

Supported by grant 20332 from the National Fonds voor Wetenschappelijk Onderzoek, Belgium.

Presented at the 50th Scientific Sessions of the American Heart Association, Miami Beach, Florida, November 1977.

Address for correspondence: Boudewijn Denef, M.D., Department of Pathophysiology, University Clinic Sint-Raphael, Capucijnenvoer, 3000 Leuven, Belgium.

Received February 2, 1979; revision accepted May 15, 1979.
Circulation 60, No. 6, 1979.