Power Spectrum Analysis of Heart Rate Fluctuations: The Renin-Angiotensin System's Role as Short Term Cardiovascular Control System

by

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ABSTRACT

By applying random process analysis of beat-to-beat fluctuations in heart rate, we report a quantitative noninvasive means of assessing the renin-angiotensin system's role as a rapidly reacting cardiovascular control system. In addition, simultaneous analysis of arterial blood pressure fluctuations demonstrates the close coupling of the two channels. This data provides new evidence that as a short-term cardiovascular control the renin-angiotensin system plays an important role.

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Introduction

The term homeostasis is used by physiologists to mean maintenance of static, or constant, conditions in the internal environment. Essentially all the organs and tissues of the body perform functions that help to maintain these constant conditions. The control systems of the body act by a process of negative feedback. In general if some factor becomes excessive or too little, a control system initiates negative feedback, which consists of a series of changes that returns the factor toward a certain mean value, thus maintaining homeostasis.

My dissertaion is concerned with the regulation of cardiac function by the renin-angiotensin system. By employing spectral analysis of heartrate and blood pressure fluctuations we have been able to assess quantitatively the level of control on these parameters by the renin-angiotensin system. This new application of well established techniques will provide new insight into regulation of cardiac output, respiratory control and other related systems.

An additional benifit of spectral analysis is the determination of the time response of the renin-angiotensin system. We have observed major effects in the low frequency content of the power spectrum with varying activity of the R-A system. This would imply that the R-A system can respond as a short-term control system (previous work had labeled this system an intermediate-term system).

Future refinements of these techniques will enable the physician to assess non-invasively the reflex-control of many physiologic systems. This potential clinical tool may help to eliminate the guesswork often employed when titrating delicate cardiac medicines.

In addition it will be possible to evaluate the development of the autoregulatory systems. Syndromes which may represent a breakdown or disfunction of proper development could be diagnosed before current clinical methods of observation would be able. It is in these ways that we expect this research to develop.

REVIEW OF CARDIOVASCULAR REGULATION

: Regulation of Cardiac Output

The primary purpose of the heart as a working organ is to move blood about the body so that various substances may be transported from one region to another. Exercise, stress, and other periods of heavy demand may require that cardiac output increases to six times the resting level. More subtle changes in cardiac output are observable within the steady resting state. Normal respiratory activity, one example, has long been recognized as an inducer of heart rate changes.[5,8,9,10]

There are both intrinsic and extrinsic mechanisms to adjust the heart to the working requirements. Here a very brief overview of the various systems will be discussed. More detailed presentations of these mechanisms are covered in texts of mamalian physiology, and in particular Guyton's Medical Physiology 5th Edition.

The two basic means by which pumping action is regulated are:

i. intrinsic autoregulatio

ii. reflex control - via autonomic nervous system.

Intrinsic autoregulation is also known as the Frank-Starling Law of Cardiac Pumping. Simply stated, within normal operating limits, the heart pumps all the blood that is supplied to it. Due to an increased stretching of cardiac muscle efficiency is gained and a corresponding increase in contraction force expels the extra fluid. Reflex control-via autonomic nervous system is perhaps the most striking of the control systems. There are two very important features of nervous regulation of the circulation; first, reflex control can respond within two to three seconds; second, large

parts of the circulation may be controlled simultaneously by nervous action.[6] The two nervous mechanisms we examine are the sympathetic system and the parasympathetic system.[16] Within the limits of this introduction, sympathetic stimulation tends to increase heart rate and also force of contraction while parasympathetic stimulation decreases heart rate and , to a lesser degree, decreases force of contraction.

The flow to any tissue of the body depends on the ratio of the driving force divided by the resistance.

$$\overset{*}{Q}=\frac{\text{Pressure}}{\text{Resistance}}$$

Two separate systems for localized tissue regulation,

i. Nervous innervation of small vessels

ii. Humoral regulation of the circulation

regulate blood flow through the tissues by altering the resistances of the small vessels. The sympathetic nervous system is very important in this function. Either by directly stimulating nerves in the vessels or by causing the secretion of certain hormones which constrict these vessels a <u>tone</u> or partial state of contraction is maintained. Changing the level of stimulation can thus increase or decrease vascular resistance.[1,23]

In addition to the sympathetic system-controlled hormones, an independent system exists which operates to regulate arterial blood pressure. This system, the topic of this thesis, will now in detail be introduced. The overall control system is displayed in block diagram form on page 35.

: The Renin-Angiotensin System

As early as 1898, it was found that crude saline extracts of the kidney contained a substance which increased arterial blood pressure which was then named renin. Little interest was paid to this discovery until 1934, when Goldblatt showed that persistent hypertension was produced when renal arteries were constricted. Renin thus came to occupy a central position in the field of experimental hypertension.

Renin, by itself, does not directly increase blood pressure. Independent studies by Braun and Menendez (1940)[3] and also by Page and Helmer (1940)[18] showed that renin was an enzyme which acts on a specific substrate present in the plasma. Braun and Menendez named this active blood pressure regulator hypertensin, while Page and Helmer called it angiotonin. Today we call this substance angiotensin.

The formation of active angiotensin, as illustrated on page 36 in vivo is a complex process that is initiated when the enzyme renin acts on the substrate angiotensinogen, a plasma globulin belonging to the α_2 fraction, to yield a decapeptide known as angiotensin I. While pharmacologically inert Angiotensin I, through the action of further enzymes present in the plasma, is converted to an active octapeptide, Angiotensin II. The majority of the conversion takes place in one pass through the pulmonary circulation.

: Effects on the Cardiovascular System

The vasoconstrictor effect of angiotensin II given intravenously is strongest in the vessels of the skin and kidney. The precapillary region is most affected, and blood flow in these regions falls sharply.

Vasoconstriction in response to angiotensin has two components: a direct action on the vascular smooth muscle and an indirect action mediated through the sympathetic vasoconstrictor outflow. The direct action accounts for most of the increase in total peripheral resistance underlying the pressor response; however, in certain vascular beds, vasoconstriction is mainly due to the sympathetic effect and is suppressed by β-adrenergic blocking drugs.

Angiotensin II has been shown to be a positive inotropic agent in vitro (Koch-Weser 1964)[15]; however, this has not conclusively been proven in vivo. The response of the cardiovascular system is dominated by the elevated systemic blood pressure resulting from the vasoconstrictor activity of angiotensin II. Baroreceptor reflexes slow cardiac rate, but due to a central parasympathetic inhibition by angiotensin II, this slowing is not as dramatic as if an α receptor agonist had raised the blood pressure by a similar amount.[17]

Angiotensin II is by far the most powerful pressor agent, an activity about forty times that of norepinephrine. Bolus intravenous injections cause rapid pressure rises and normal state is returned to in a matter of minutes. Continuous infusions will maintain elevated levels for hours or days.

: Role in Circulatory Homeostasis

Historically the vasoconstrictor effects of renin and angiotensin have commanded the most attention. There is evidence that a variety of experimental manipulations lowering blood pressure cause the release of renin, thus a physiological role of renin in the regulation of cardiovascular homeostasis is suggested.

Repeatedly it has been shown that factors that lower blood pressure (or volume) increases renin output. Likewise increasing blood pressure (or volume) has the opposite effect. These changes in renin output, with changing pressure, may be attributable to changes in renal arterial perfusion pressure acting directly within the kidney. (Mechanically restricting blood flow causes increased renin output, confirming this notion.)

There is no simple relation between renin levels and blood pressure. Electrolyte balance, sensitivity of the blood vessels to constrictor effects, dietary restrictions, salt retention are all factors that contribute to the picture. Figure 3, on page 37 , attempts to portray some of these speculations on the possible homeostatic role of the renin-angiotensin system.

: Effector Hormones

Angiotensin II - octopeptide -- three very striking physiological actions: 1) constriction of the arterioles
2) causes sodium retention (by acting on kidney)
3) acts on adrenal cortex to evoke an increase in aldosterone secretion.

Aldosterone - adrenal corticosteriod -- chemically unique among steroid hormones because of its 18-aldehyde configuration. Aldosterone is the most potent natural mineralocorticoid acting primarily on the renal tubules to increase the reabsorption of sodium with chloride and to promote the elimination of potassium ions. Aldosterone undoubtedly plays a major role in regulating sodium and potassium homeostasis.

In the operation of the renin-angiotensin-aldosterone system the regulation of sodium balance and extra-cellular fluid volume are interconnected with blood pressure so that regulation of these functions can be viewed tentatively as a single coordinated process. The R-A-A system appears to regulate sodium balance, fluid volume, and blood pressure as follows: The kidney, when its perfusion is threatened, releases renin. Renin induces the liberation of AII from a circulating plasma globulin. AII, in turn, stimulates aldosterone secretion. Angiotensin and aldosterone act to raise arterial pressure and to promote sodium retention. This positive sodium balance leads to a secondary retention of water and an expansion of extracellular fluids. These induced changes operate together to raise the blood pressure and restore renal perfusion, thus compensating the system and shutting off the initial signal to renal renin release. We portray this regulation on page 38: Figure 4.

Data illustrating the above effects of Angiotensin II have generally been obtained in acute settings. Mechanical constriction of arteries, salt depriving diets, and other such manipulations serve to change the normal operating levels of the renin-angiotensin system. Our studies will focus on the normal levels in the conscious dog with normal salt intake.

MATERIALS AND METHODS

A. Dogs. We conducted a series of experiments on non-anesthetized trained adult mongrel dogs using techniques developed by Dr. A. Clifford Barger and associates.[7,19,20,21] Several mongrel dogs (30 ± 4 kg) were used in these experiments. Each dog was housed in a metabolic cage and subjected to a three week training and conditioning program. During this program trained veterinary assistants screened each dog for parasites, and any grossly observable abnormalities. Any dog with untreatable parasites, heartworms, or any physical abnormality was rejected. Quarantine was maintained for 21 days, during which time no surgical interventions were performed. Each dog was outfitted with a cotton jacket and introduced to the experiment area. Over the course of 10 to 20 days the animal was conditioned, through reward, to lie perfectly still for periods of two hours or longer. Comfort was enhanced through use of a four-inch foam mattress pad and a climate controlled, air conditioned room. Quiet was maintained at all times both during conditioning and during experiments. Dogs who failed conditioning were rejected.

Diet was administered once daily by animal technicians. Three different diets were maintained depending on the

desired sodium intake. Respond 1200 Brand dry chow was used to maintain high ($\cong$ 100 Meq/day) salt intake, while Hills H/D can chow was used to fix a low salt intake ($<$ 10 Meq/day). Combinations of above chows could thus fix salt level at the normal intake level ($\cong$ 70 Meq/day). Diet was maintained for 14 days prior to experiment to assure stability of salt depletion.

B. Surgical Procedures. After the aforementioned training and screening period, the animal was ready for instrumentation. The animals were anesthetized with sodium pentabarbitol (30 mg/kg I.V.), and intubated with balloon cuff endotracheal tube. A Harvard Apparatus ventilation pump was available if mechanical ventilation was required.

Two different procedures were performed. The first was a femoral arterial and venous catheterization. The right inguinal area was thoroughly shaven and prepped with IO surgical scrub. The vessels were exposed by careful dissection and stay sutures were passed underneath. A pursestring was sewn in the wall of the vessel using 4-0 cardiovascular silk suture. Within the circumference of the pursestring a small hole was cut in the wall of the vessel. Retraction anteriorly and posteriorly prevented flow out the hole. Tygon tubing 40/70 gauge was entered through this hole and advanced approximately six inches. The catheters were specially prepared with two 'collars' about 8 inches from the tip. The collars consisted of

identical, (but larger) polyvinyl tubing adhered by cyclohexanone. The collars provided a simple but effective method for securing the catheter to prevent accidental removal. The catheters were exteriorized through subcutaneous tunnels, sealed with metal obturators or two way plastic stop cocks, and protected by a cotton jacket as previously mentioned. This catheterization procedure was nontraumatic and does not occlude the vessels.

The second type of operation is more involved. Positioning the animal on his left side, an area from sternal midline to vertebral midline was shaven and prepped. A right lateral thorecotomy in the fourth intercostal space was performed using electrocautery. Care was given to not puncturing lung tissue. Positive end-expiratory pressure (3-4 cm H_2O) was maintained throughout this part of the procuedure. The incision area was retracted using a Codman chest retractor. The azygous vein was exposed and in a similar manner to the femoral vessel catheterization, a polyvinyl catheter was inserted. The tip of the catheter was measured to fit in the SVC and in this manner, CVP could be measured. In addition the internal mamillary artery and vein were exposed. Catheterization of these vessels, due to their small diameter, required ligation and thus occluded flow. Collateral vessels served to replace the loss of blood transport in the immediate area.

Three Medtronic epicardial pacing electrodes were attached in the following manner: Pericardial tissue was opened longitudinally, with care not to cut phrenic nerve, and epicardial tissue exposed. Pacing wires were screwed in at the right lateral side of the right atrial appendage, the right lateral wall of the mid-right atrium and the mid-anteriolateral wall of the right ventricle. The screws were anchored using four 4-0 cardiovascular silk sutures. The catheters were exteriorized through subcutaneous tunnel and protected by a cotton jacket. To close the fourth intercostal space we used sterile umbilical tape to approximate the ribs. Chromic suture in a continuous manner was used to close subcutaneous layers and skin. The femoral incision usually required minimal postoperative care; by using continuous chromic skin sutures, the dog did not try to bite at the stitches. Infection was prevented by a prophylactic antibiotic treatment; 250 mg ampicillin was administered PO QID for 10 days. In addition, IM gentamycin 80 mg BID for 5 days complemented the ampicillin. The right flank incision required more care. Topical dressings (nitrofurizone cream) was applied at least daily until the wound fully healed. Gauze sponge 4 x 4's were used to protect the wound from abrasion in the early stages of healing. To prevent clogging of the pressure lines daily maintenance of these catheters was required. First 3 ml of blood, saline and heparin is

withdrawn sterilly by syringe. Fresh sterile saline is injected into each catheter, and, finally a heparin bolus (1000 units/ml) is injected into the catheter. The volume of the catheters was previously measured so only a small excess of heparin actually ever gets into the animal's circulation. The high concentration of heparin in the cannula prevented clotting for 24 hours. If a clot did happen to develop, thrombolysin provded by Merck Sharp and Dohme was infused by Harvard pump to open the catheter. The daily flushings were accompanied by the short training period. This daily reinforcement made animals very secure with experimental procedure, room and table. All animals were fully recovered before experimentation was undertaken.

C. Hemodynamic Measurements. Fluctuations in heart rate, respiratory rate and tidal volume, arterial and central venous pressure were studied. Precision was of the utmost importance, any error would reflect itself in the statistical analysis. Our laboratories, at the Harvard Medical School and Massachusetts Institute of Technology were equipped with state of the art instrumentation to accomplish this control. Briefly, I will mention the equipment used and methods employed.

Dr. Barger's laboratory (Harvard Medical School Department of Physiology) is equipped with two examination rooms in which experiments were carried out. Each room contained a padded table on which the animal would lie.

Arterial pressure was measured in the recumbent dog with a P23Db Statham pressure transducer and recorded on a Grass polygraph. The amplified signal is simultaneously inputted to an eight channel Hewlett-Packard FM instrument tape recorder. Electrocardiograph is monitored by surface limb leads and amplified in a similar manner. A pneumograph tube is used to monitor respiratory frequency. At the Massachusetts Institute of Technology we use facilities of the Division of Laboratory Animal Medicine (DLAM). There we utilize an Electronics for Medicine (Honeywell) VR-16 monitor. With three pressure channels and three ECG amplifiers we are well equipped to record the necessary signals. A Hewlett-Packard FM instrument tape recorder is likewise used to maintain permanent record of the signals. In addition to the visual display the VR16 CRT offers, we run a photographic paper record which instantly produces hard copy for immediate referral.

Calibration signals enable one to measure quantitatively absolute pressure changes as well as mean pressure. These calibration signals are recorded at the beginning of each experiment for use later in analysis.

The infusion of medications was done through use of a Harvard apparatus infusion pump. All medications were infused intravenously, lines maintained by heparinized saline flush (3units/cc). Between interventions the lines were flushed and rebalanced. In order to ensure stability

of data we made every effort to condition the dog to experimental procedure. Training helped make the animal somewhat at ease with the surroundings; however, it was vital to maintain absolute quiet throughout the experiment. This prevented distraction by the subject or artifact due to his sudden startle. A complete data run contains at least 1000 heartbeats of stationary data. We generally disallowed the first five to ten minutes immediately after an intervention as nonstationary.

Experimental protocol called for selection of least noisy ECG lead. Shielded cables were used in conjunction with Honeywell or MMM skin pads, and appropriate electrolyte gel. Areas of contact were preshaven for best contact. When using epicardial leads, care was taken to select proper polarity and lead. Atrial electrograms were preferred to ventricular ones as the digital algorithm was better able to identify this type of signal.

The Hewlett Packard tape recorder also records on audio track. Interventions were vocally recorded by the investigators on this track insuring that proper identification of steady state sections was made.

ANALYSIS

A. Computer Analysis. Computer analysis was performed on two independent systems. Initially only the RR interval time series was studied. The RR interval sequence was analyzed in the following manner. An FM tape recorder

provided a signal (the ECG) to an analog device which measured the RR intervals and punched their digitized values onto paper tape. The device electronically differentiated this signal to yield the process $\frac{dV}{dt}$, where the R wave peaks $\frac{dV}{dt} = 0$. In this way a precise indication of the R wave peak is recorded. We do, however, have to set a threshold voltage to identify RR intervals and not other peaks. The time between these R peaks is measured using a 20 MHz crystal clock as a standard. The RR intervals are displayed digitally in real time, and permanently recorded on puched paper tape to one millisecond accuracy. This accuracy is due to the sharpness of the R wave peak, but the error is sufficiently small to enable the accurate determination of the statistics and autocorrelation function of the RR interval fluctuations.

The punched paper tape was then fed to a Nova general purpose minicomputer. Using a program written by Richard Cohen, the list of RR intervals is analyzed.

The system just described is limited to analysis of RR interval fluctuations. Graphical display is very crude and operation of this system quite time consuming. In order to fully utilize our gathered data it became necessary to construct a fully automated, flexible system. Signals recorded by our Hewlett Packard #3968 are processed by a microprocessor data analysis system developed by Dr. Solange Akselrod. Presently four data channels can be

analyzed simultaneously. They are ECG, A.P., CVP, and Resp. volume. The ECG event detector algorhithm used was developed by Paul Schluter of the B.M.E.C.C.I. The analysis presented in this work included heart rate, respiratory rate, and arterial and central venous pressures. The memory of this system currently employs 48K, additional storage is on hard disc, cassette tape or reel-to-reel computer tape. This system performs spectral analysis of fluctuations in the above mentioned channels. Graphical results are via Hewlett Packard digital plotter. Integrated areas of spectral peaks are calculated by 8085 microprocessor using standard techniques.

Direct examination of results of both methods provides confirmation that the systems approximate each other. Some minor differences are noted here. First the low frequency peak area had been computed from 0.0HZ is doubtful due to DC drift. Our new system's first point has been set at 0.02HZ. Secondly, integrated areas are likely to be somewhat different. In the first method, Simpson's method was employed on a limited number of points to extimate the area of a peak. The 8085 is able to more accurately perform this method on many more points in a given band width. Thus, areas more truly represented the power in these bands. The increased accuracy is due to the radically different methods in which the computers perform the analysis. The Nova system computed spectral peaks by direct Fourier analysis

of the autocorrelation function. We now employ a system which utilizes a Fast Fourier Transform algorithm. The extent of the differences will be presented in the next section. Portions of the above computer program are attached at the end of this thesis.

B. Analytical Our primary data for the experiments on Beat to Beat cardiovascular control are the time intervals between R-R peaks. These time intervals were measured with a digital computer, as previously described. All the information about fluctuations is contained in the departure from mean value.

One method to study the characteristics of these fluctuations is to convert the list of pulse intervals into a list of instantaneous impulse rate samples. The construction of instantaneous pulse rate from pulse intervals is illustrated in Figure 5.

In the next figure we show how HR actually fluctuates in a mongrel dog (Figure 6). For any particular interval between pulses, the reciprocal of the time interval, the impulse rate is assigned to all the time between the beginning and end of the interval. In this way a frequency modulation is transformed into an amplitude modulation. The reciprocal at the time interval, the instantaneous pulse rate, is larger when the firing is faster and of course, vise versa. By sampling the instantaneous impulse rate at equi-spaced intervals of time, one obtains a list

of pulse rate samples which can be mathematically manipulated in the same way as periodically sampled continuous functions. By making 'sampling' intervals of a fine enough time grain, approximately $<$ 1/2 average interfire interval, a negligible amount of information about the statistics of the pulse train will be lost. If X(t) is a random process, then the single-time probability distribution $p(X_1)$ is just the histogram, as shown in Figure 7, on page 41.

Spectral analysis is an analytical tool developed to help in the understanding of the filtering of signals by linear, time invariant devices.[26]

A linear filter is a device which obeys the law of superposition. Suppose that $X_1(t)$ and $Y_1(t)$, are the input and output of a fixed-parameter linear system. If the input $X_1(t)$ produces an output $Y_1(t)$, then it will produce the output $AY_1(t) + BY_2(t)$ when the input is $AX_1(t) + BX_2(t)$. Suppose an input to a linear filter is $X(t) = e^{iwt}$. The time translated input is $X(t + \tau) = e^{iw(t + \tau)} = e^{iw} X(t)$. Or this can be written

$ax(t)$ where $a = e^{iwt}$ independent of t

therefore: $y(t + \tau) = ay(t)$ because filter is linear. When condition t = o is imposed, $y(\tau) = y(o)e^{iwt}$ proving that the output function is merely the input function multiplied by a constant. Given any time invariant linear filter, one can characterize it by specifying the response

to a unit amplitude sinusoidal signal at each frequency. By expressing a deterministic function as a weighted sum of sinusoidal functions of time, as is shown in Figure 8, on page 42, one derives the Fourier analysis of the function. A stochastic process is an ensemble of time functions which have some average properties in common, but which cannot be determined exactly as a function of time. One average property of a stochastic process is its autocovariance. Defining the autocovariance as the average product of the deviation of a random variable from its mean, multiplied by the value of the deviation later in time, we note that the autocovariance is a continuous deterministic function of time: which depends on the time lag τ.

In formula let X(t) be a stochastic process with mean value $\bar{X}$ we have defined the autocovariance as

$$\overline{(X(t) - \bar{X})(X(t + \tau) - \bar{X})}$$

thus at $\tau = o$ we have $\overline{(X(t) - \bar{X})^2}$ which is the variance. The variance spectrum is a plot of the value of the weighting factors and frequency. The value of the variance specturm at a particualr frequency represents the contribution of that frequency to the total variance of the stochastic process.

An alternate method of obtaining the power spectrum or variance spectrum, of a stochastic process is from direct Fourier analysis of the individual time functions which

are members of the ensemble of functions which constitute the stochastic process.

Spectral analysis is often performed on continuous functions of time which have been sampled at equally spaced points in time. By this procedure a list of numbers, which are the values of the continuous function at the sample times, is generated. The power spectrum of this list is done by digital computer with a Fast Fourier Transform (FFT) subroutine (Cooley, Lewis and Welch 1967). The Fourier transform is a list of complex numbers, each number associated with a particular frequency. One calculates the amplitude of each of these numbers and squares it. This list of squared amplitudes, at a number of evenly spaced points in the frequency domain, is the variance spectrum. The power spectrum and autocorrelation are related to each other by a Fourier transform.

$$S(\nu) = \text{Fourier Transform of } R_{xx}(\tau)$$

$$S(\nu) = \frac{(X(t) - \bar{X})(X(t+\tau) - \bar{X})}{(X(t) - \bar{X})^2}$$

The power spectrum of any stochastic process is related to the autocorrelation of the process. The autocorrelation is defined as the autocovariance divided by the variance. Thus, the autocorrelation is unity at zero time lag, and varies with time lag, typically becoming zero as the time lag becomes large. Thus the autocorrelation is a measure of the system's memory, or to what degree the

value of the process $X(t + \tau)$ is correlated with the value of the process at time t. In formula: autocorrelation of the impulse rate, X(t) is

$$\frac{\overline{(X(t) - \bar{X})(X(t + \tau) - \bar{X})}}{(X(t) - \bar{X})^2} .$$

RESULTS

In order to characterize mathematically the physiologic mechanism which produces fluctuations in heart rate and blood pressure we look closely at the power spectrum of the system.[4,22] Here is presented for examination the power spectrum analysis from eight different experiments. Each of the eight experiments produced a baseline spectrum, that is, the spectrum from data sampled just prior to the administration of a blocking agent. The six converting enzyme experiments also produced spectrum from data during renin-angiotensin system blockade. The final two experiments (Xenon 6/19/80 and Xenon 6/21/80) investigate blockade with Saralasin (1 Sar 8 Ala Angiotensin II). These experiments have power spectrum from several different doses of Saralasin (.1, .5, 1.0, 5.0, 10 μg/kg/min).

The results of each experiment have been tabulated in the following manner. Computer analysis by 8085 system produces a hard copy of spectrum via Hewlett Packard plotter. These graphs are presented here in original form. The computer will also calculate the area under the spectrum for any given bandwidth. The bandwidth of the peaks was determined by inspection of these plots. Representative areas for Low, Mid and High frequency peaks have been bar graphed for each experiment. In addition, the numerical figure is recorded in tabular form for each experiment.

By examination of Figure 9, on page 43, which represents the power spectrum of heart rate fluctuation in

the dog without renin-angiotensin blockade, we see the three peaks described in the human by Sayers.[22] In any of the following spectra, one or more of the three peaks may not be evident because of low amplitude or overlap. The high frequency peak will not be present if the respiratory rate exceeds the mean heart rate.

In the baseline state we see quite different looking HR power spectra from date to date. In particular we notice that the high frequency peak moves as the respiratory rate changes. A highly irregular respiratory rate will produce a broad, low peak while a regular respiratory rate will produce a more defined peak.

The arterial pressure power spectrum sometimes displays a fourth very high frequency peak. The area of these peaks has also been computed and recorded on the data sheets.

Examination of all eight low frequency peak areas for baseline heart rate power spectrum shows enormous variation. Day to day changes in the dog's natural state, exciteability, etc., can account for this. Meaningful results can be obtained by comparison of power spectrum from data sections of similar state. To comply with this requirement we will not make reference to a single power spectrum but rather to the relative change in the area of a peak or peaks with addition of a blocking agent, done immediately after obtaining baseline data.

The attached data sheets and computer drawings show

areas of the three peaks for our eight experiments. With the exception of Tabes March 6th 1980, the areas were computed directly by the microprocessor. I have taken generally the limits of the integrals to be .02 to .09 Hz and .09 to .20Hz for Low and Mid frequency peaks respectively. The High frequency peak of course changes with respiratory rate. The first Bohr experiment doesn't have a pronounced high frequency peak. This dog had a tendency to pant very rapidly; thus his respiratory rate was considerably higher than resting heart rate.

Results of peak area changes with converting enzyme inhibitor blockade are most interesting in the Low frequency heart rate power spectrum peak and the Low frequency arterial blood pressure power spectrum peaks. Illustration of peak area changes are presented for each experiment. In the resting dog on a normal salt diet (70 Meq/day) blockade leads to little or no change in mean heart rate or mean arterial pressure. Results presented now demonstrate that even without gross changes in HR or $\overline{BP}$ dramatic alteration in low frequency heart rate fluctuations and low and mid frequency blood pressure fluctuations are clearly indicated.

Of the six converting enzyme inhibitor (CEI) experiments five out of six cases showed an increase in the area under the low frequency peak in the heart rate fluctuation power spectrum. A graph of these results is presented here (Figure 10) for illustration. The sixth case produced

contradictory results; however, during that experiment, total blockade of the renin-angiotensin system was not achieved.

As mentioned, the arterial blood pressure fluctuations also showed interesting results with converting enzyme inhibitor blockade. The area of both the low frequency and mid frequency peaks show a clear effect in the blocked state. In comparison to baseline spectra, we note an impressive across-the-board increase in the low frequency peak with blockade of the renin-aniotensin system. Likewise the mid frequency peak also shows uniformly a slight but consistent increase from baseline. We have included bar graphs illustrating these effects on pages 44,45 and 46.

Xenon 6/19/80 was our first saralasin experiment. Dosages of Saralasin, delivered by infusion pump, in the following amounts were studied.

Baseline: No saralasin

1st Intervention: 0.1 μg/kg/min

2nd Intervention: 0.5 μg/kg/min

3rd Intervention: 1.0 μg/kg/min

The areas of the low frequency heart rate power spectrum show mixed results. At low dosages of Saralasin, the area of this peak actually goes down (compared to baseline) while the high dose shows the reverse (see bar graph on page 72,82. The low frequency peak area is twice that of

baseline with this high dose, a result which is consistent with out expectations and previous work with CEI. The arterial blood pressure fluctuation spectrum is likewise ambiguous. Increased dosages of Saralasin increase the area of the low frequency peak but decrease the area of the mid frequency peak.

Xenon 6/21/1980 follows the same protocol as Xenon 6/19/80 but dosages of saralasin are increased by a factor of ten. In this experiment, the low frequency peak dramatically increases (in HR spectrum) and shows an increase at high dosage in the BP spectrum at low and mid frequency. In addition, we see a general trend of increased power at all frequencies with increased levels of Saralasin.

DISCUSSION

These studies show that renin-angiotensin blockade selectively affects the spectral frequency content of RR interval fluctuations as well as the arterial blood pressure fluctuations. The data presented here may be analyzed in terms of a block model for heart rate control which is provided on page 35

The sympathetic and parasympathetic nervous systems are directly responsible for modulating heart rate in response to fluctuations in sensed variables such as arterial blood pressure. However, the response time of the parasympathetic nervous system is much shorter than that of the sympathetic nervous system.[25] Therefore only the parasympathetic nervous system reacts rapidly enough to mediate high frequency fluctuations in heart rate corresponding to the mid and high frequency peaks of the spectrum. Both the sympathetic and parasympathetic systems are capable of mediating heart rate fluctuation in the range of the low frequency peak. Thus the change in power spectrum of heart rate fluctuations with autonomic blockade can be understood simply in terms of the band-pass properties of these systems.

From previous experiments it appears that the direct respiratory influence on heart rate fluctuation is mediated through the parasympathetic nervous system.[2] We also suspect that the low frequency peak in the heart rate power

spectrum probably originates from fluctuations in peripheral vasomotor tone, leading then to changes in central venous and arterial blood pressures.[13,14] This low frequency component of HR fluctuations may be mediated through either the sympathetic or parasympathetic systems.

The data just presented indicates strongly that the tonic activity of the renin-angiotensin system normally damps the amplitude of these fluctuations in peripheral vasomotor tone; blocking the renin-angiotensin system leads to a large increase in the amplitude of these fluctuations in vasomotor tone and thus the perturbations to sensed blood pressures. These larger blood pressure perturbations occuring at frequencies of about .04 Hz, are in turn translated into heart rate fluctuations at these frequencies through the mediation of the autonomic nervous system.

This data strongly suggests that in conditions of normal salt intake the renin-angiotensin system can play an important role in promoting the short term stability of the cardiovascular system. This supercedes work which suggested that the renin-angiotensin system could only produce significant changes in the salt-deprived animal.

Converting Enzyme Inhibitor (CEI) very effectively stops the Angiotensin I Angiotensin II reaction. Saralasin produced inconsistent results; thus, a possible explanation rests on the type of inhibitory action Saralasin affects. 1 Sar 8 Ala Angiotensin II is an analog

of Angiotensin II. N. K. Hollenberg demonstrated that in normal man, Saralasin is a partial agonist, inducing an angiotensin-like response in settings in which endogenous AII is at a low level, and displaying dominant antagonist activity in settings in which endogenous AII levels are high.

If this statement is true, then low infusion rates of 1 Sar 8 Ala Angiotensin II should be viewed as if an infusion of Angiotensin II was given. Instead of a blocking effect we would see a stimulating effect. Slight increases in blood pressure due to increased vasoconstriction would likely appear and the heart rate power spectrum would exhibit paradoxical results. This is in fact what one observes in the Xenon experiments. At low dosages of Saralasin we did find that the HR fluctuation spectrum indeed went down in area compared to baseline. As the dose rate was increased to ten times the level one observes the area of the low frequency spectrum increase. This higher level of saralasin thus demonstrates the dominant antagonistic role.

Saralasin (1-Sar 8-Ala AII) is not the optimal blocking agent for these studies. We have thus continued using CEI as our renin-angiotensin system blocking agent. Saralasin does stimulate some interest, however. To further study this analog in a more precise manner, simultaneous infusions of AI or AII would help in the sorting out of this paradox.

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TABLE OF FIGURES

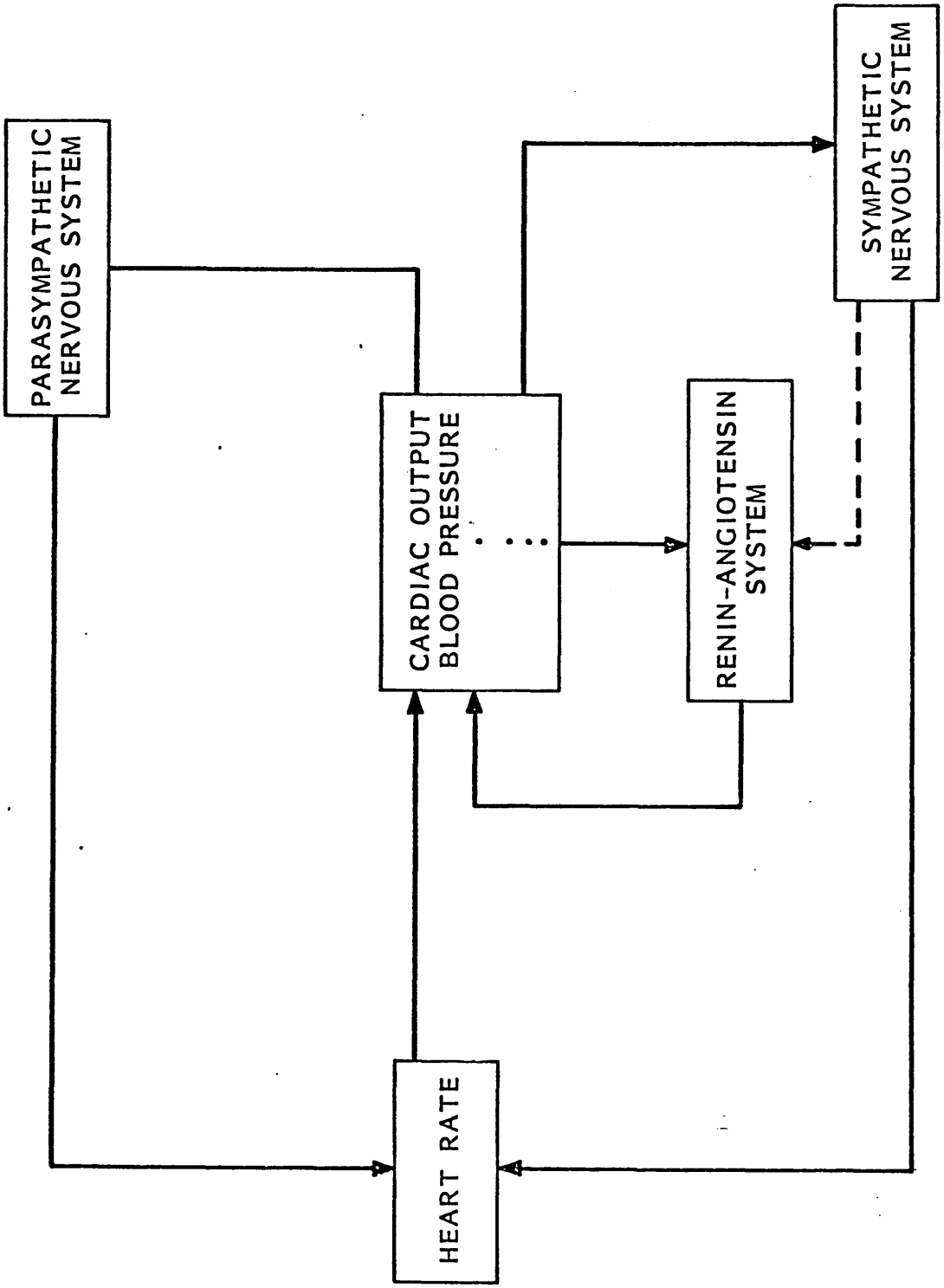
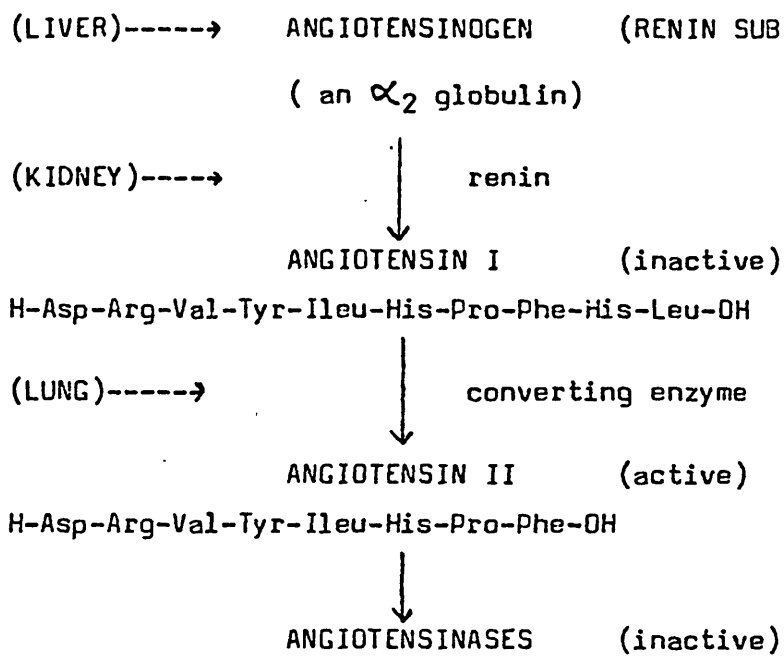


FIGURE 1 : Block diagram of short term cardiovascular control.



Note: A slight variation in amino acid composition is present from species to species.

FIGURE 2 : The Composition and Formation of Angiotensin

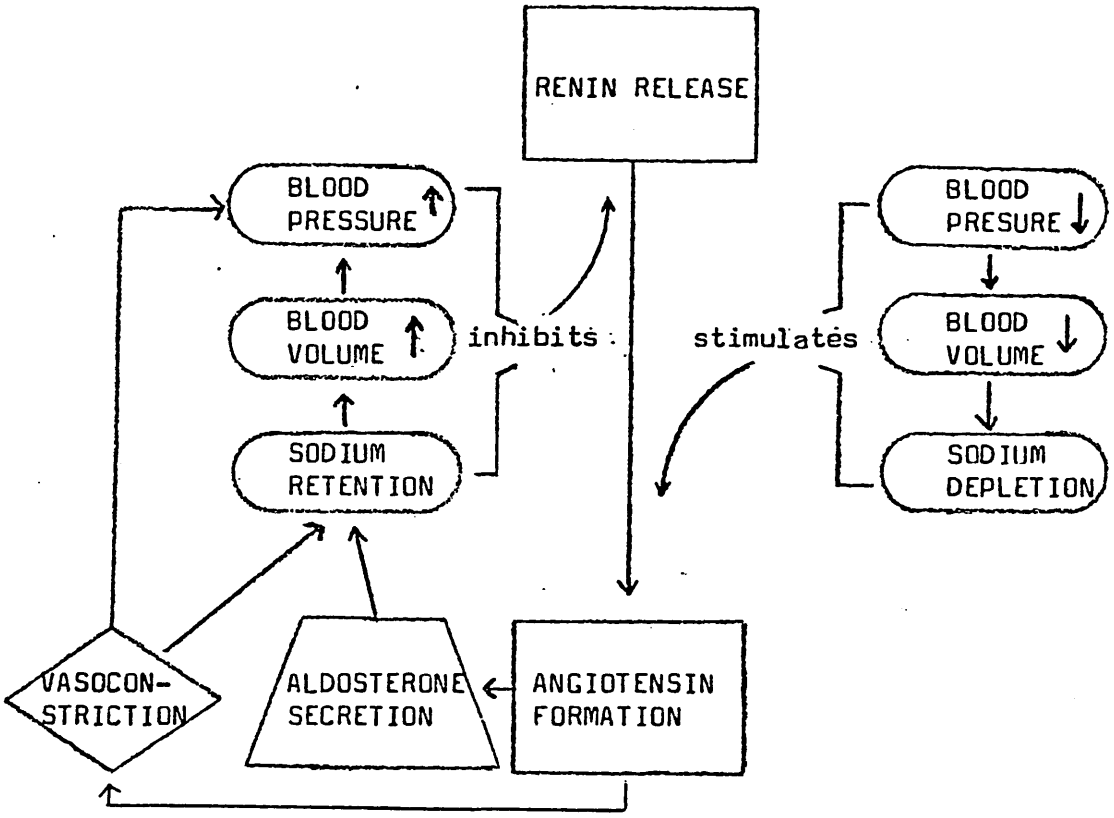


FIGURE 3 : Renin-Angiotensin System's Role in Homeostasis

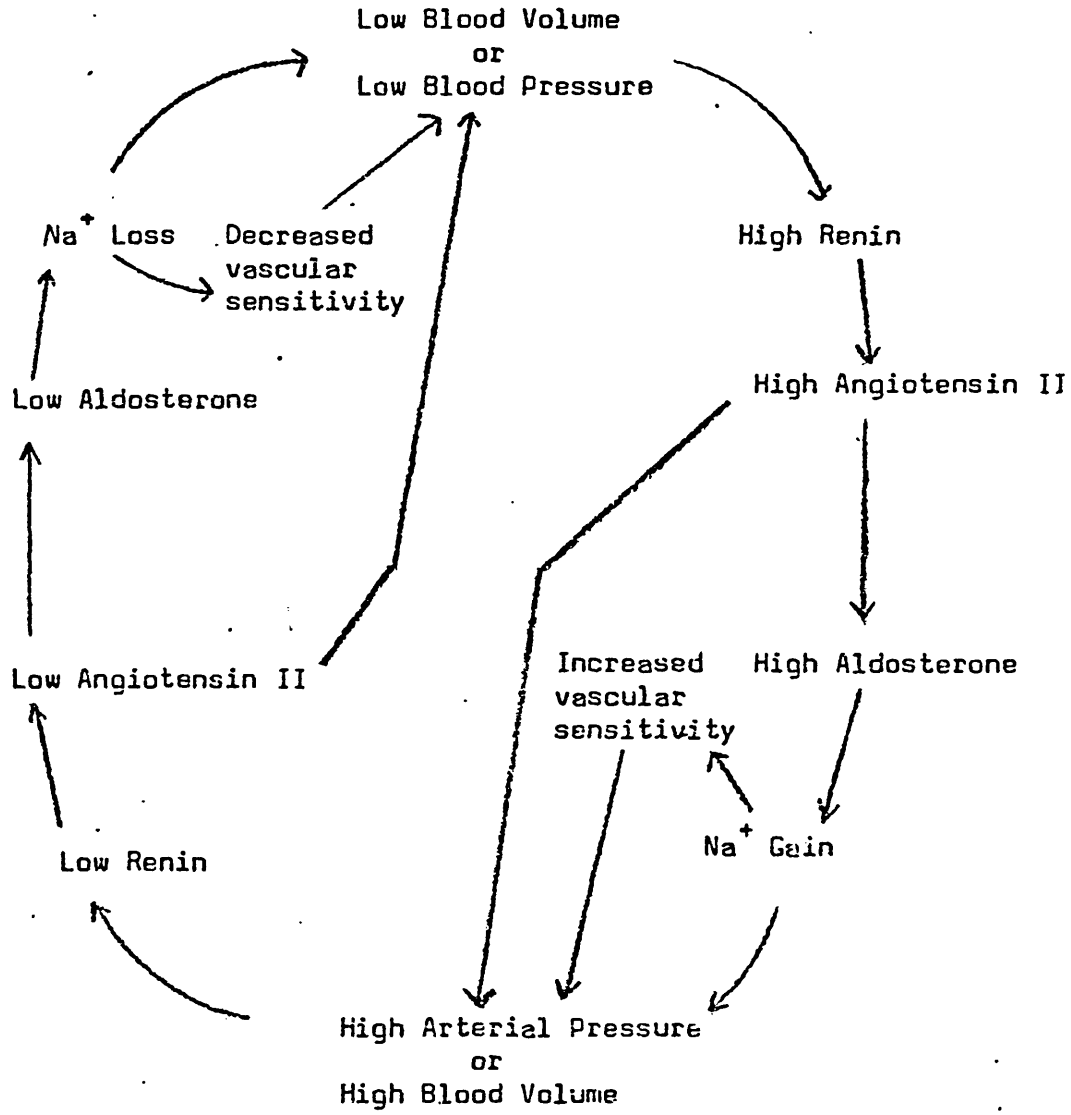


FIGURE 4: Renin-Angiotensin-Aldosterone System,

Regulation of Sodium Balance

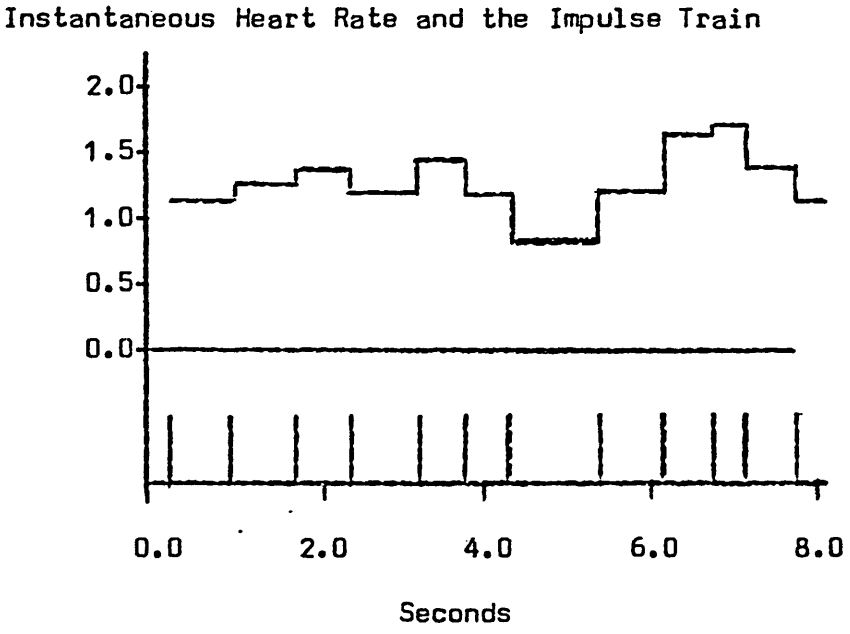
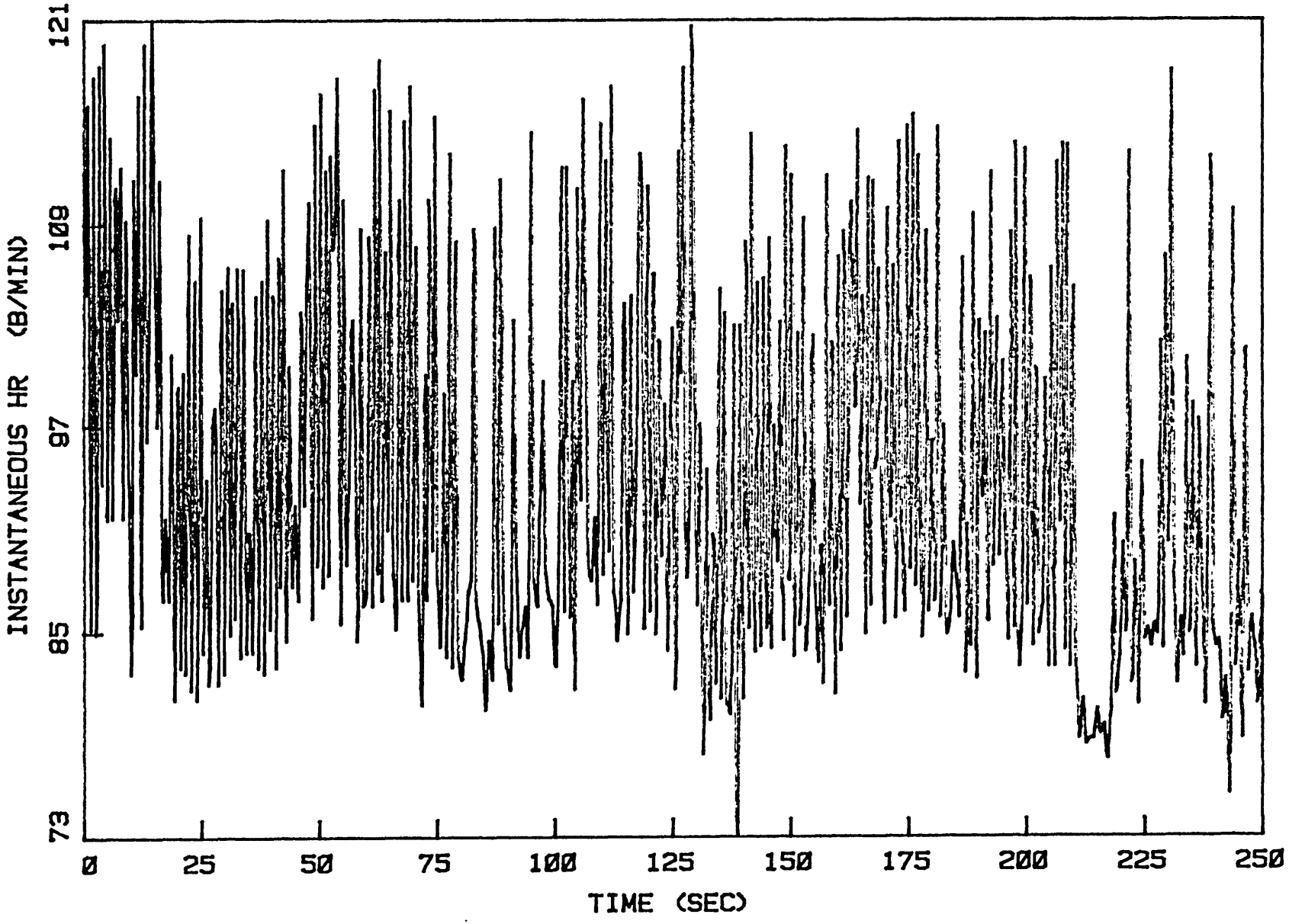


Figure 5 : Instantaneous Heart Rate and the Impulse Train The computation of impulse rate is demonstrated in this picture. During the interval between two pulses the impulse rate equals the reciprocal of that interval.

FIGURE 6

Instantaneous Heart Rate Fluctuations In The Adult Dog



RANDOM PROCESS ANALYSIS

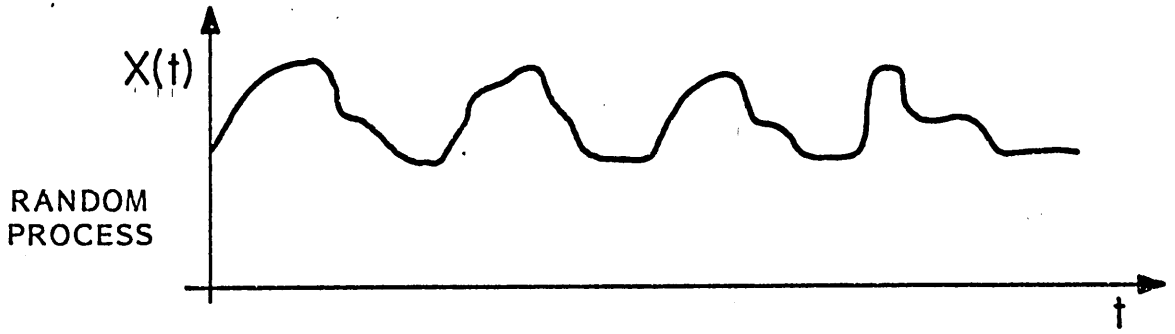
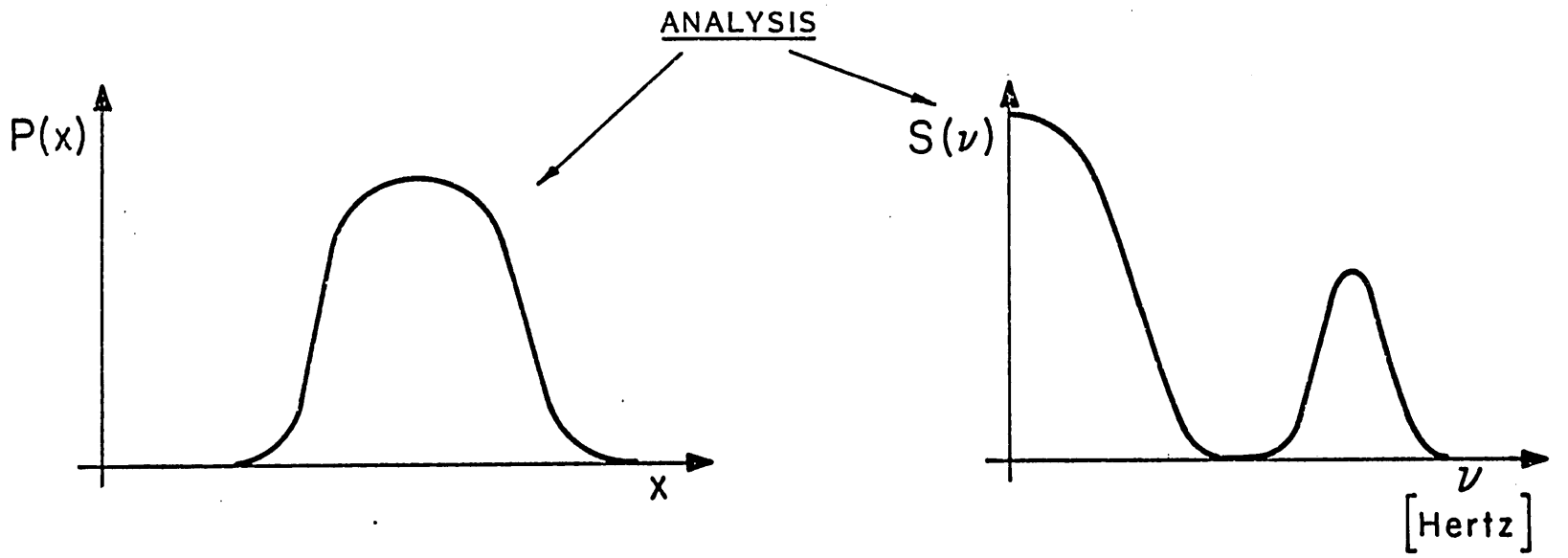


FIGURE 7



HISTOGRAM: AMPLITUDE INFORMATION

POWER SPECTRUM: TIME INDEPENDENCE INFORMATION

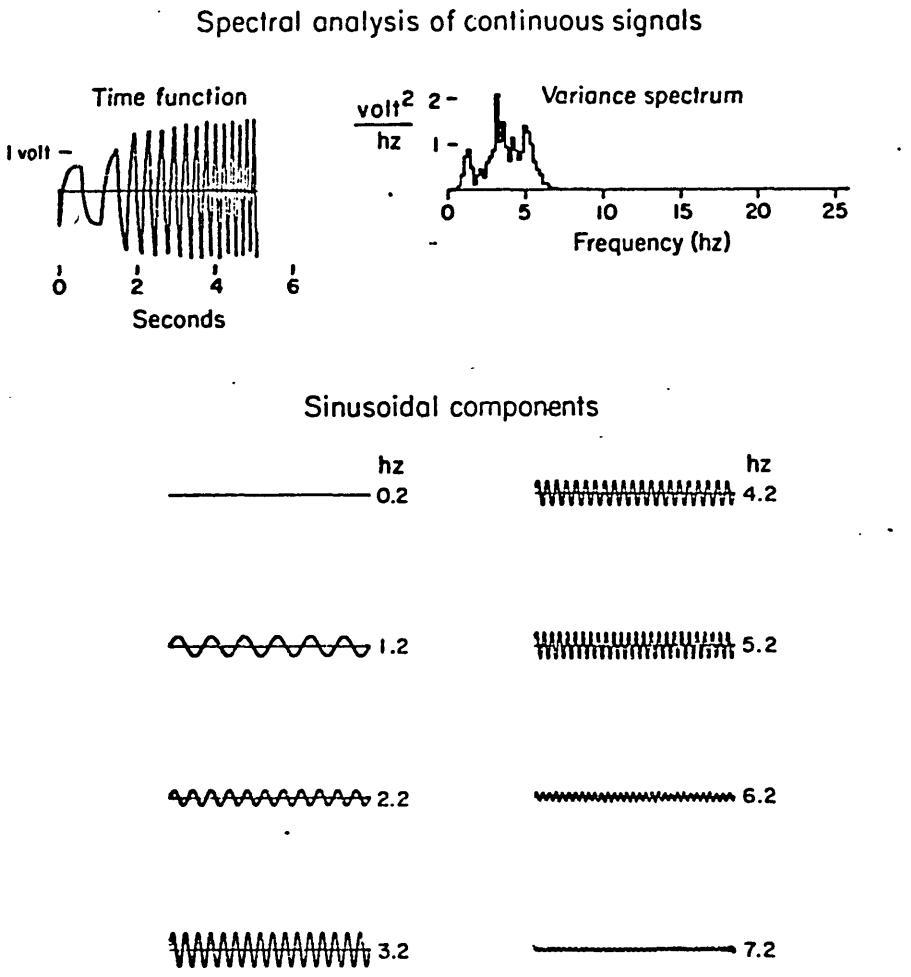


Figure 8 Spectral Analysis of Continuous Signals. An arbitrary deterministic signal is shown with the sine waves which sum to form it. The relative strength of each sine wave in the sum is shown in the variance spectrum. The variance spectrum is the squared amplitude of each sinusoidal component, as a function of frequency.

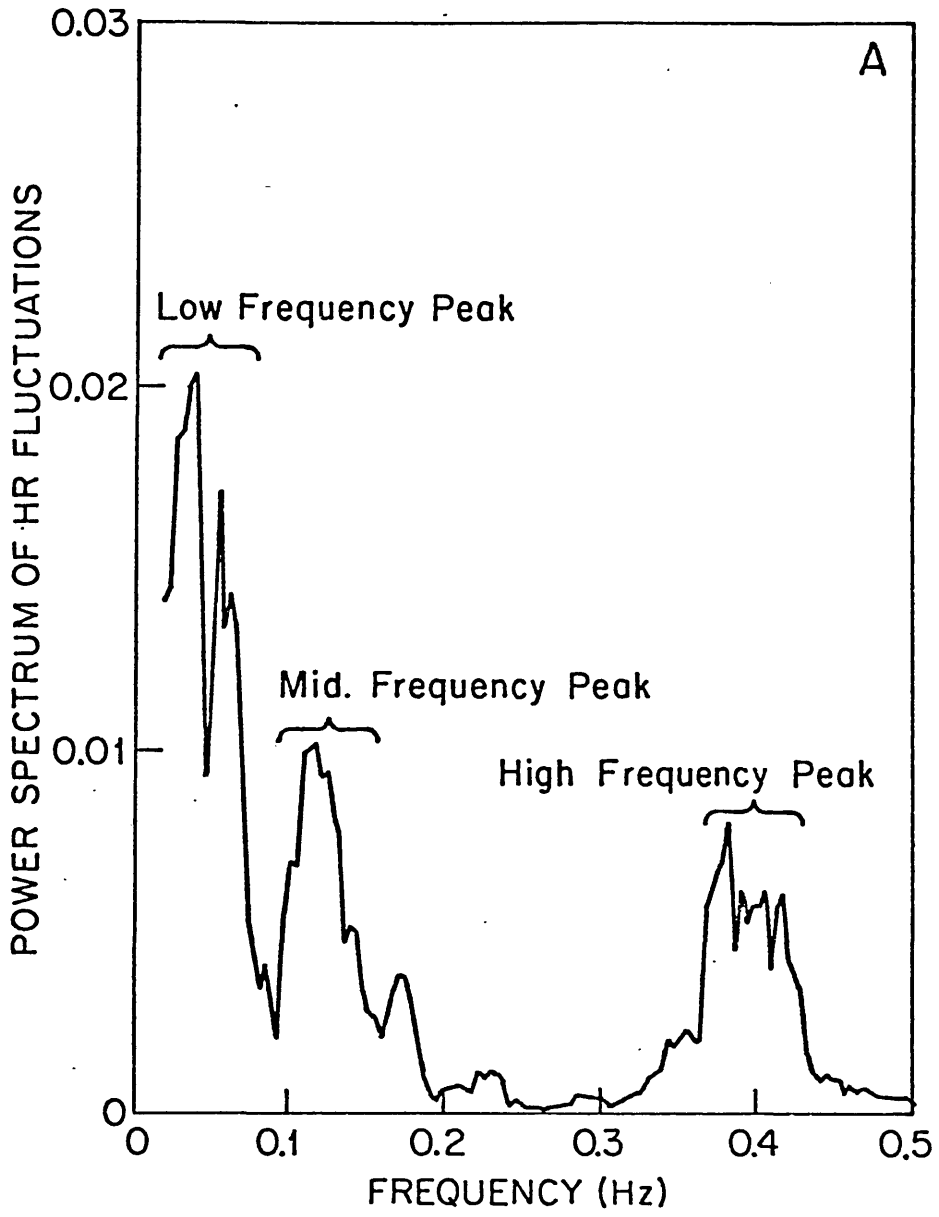


FIGURE 9 Power spectrum of heart rate fluctuations in the adult conscious dog. Power spectrum is normalized so that the integral of S(v) is the variance of the heart rate fluctuations divided by the square of the mean heart rate.

FIGURE 10

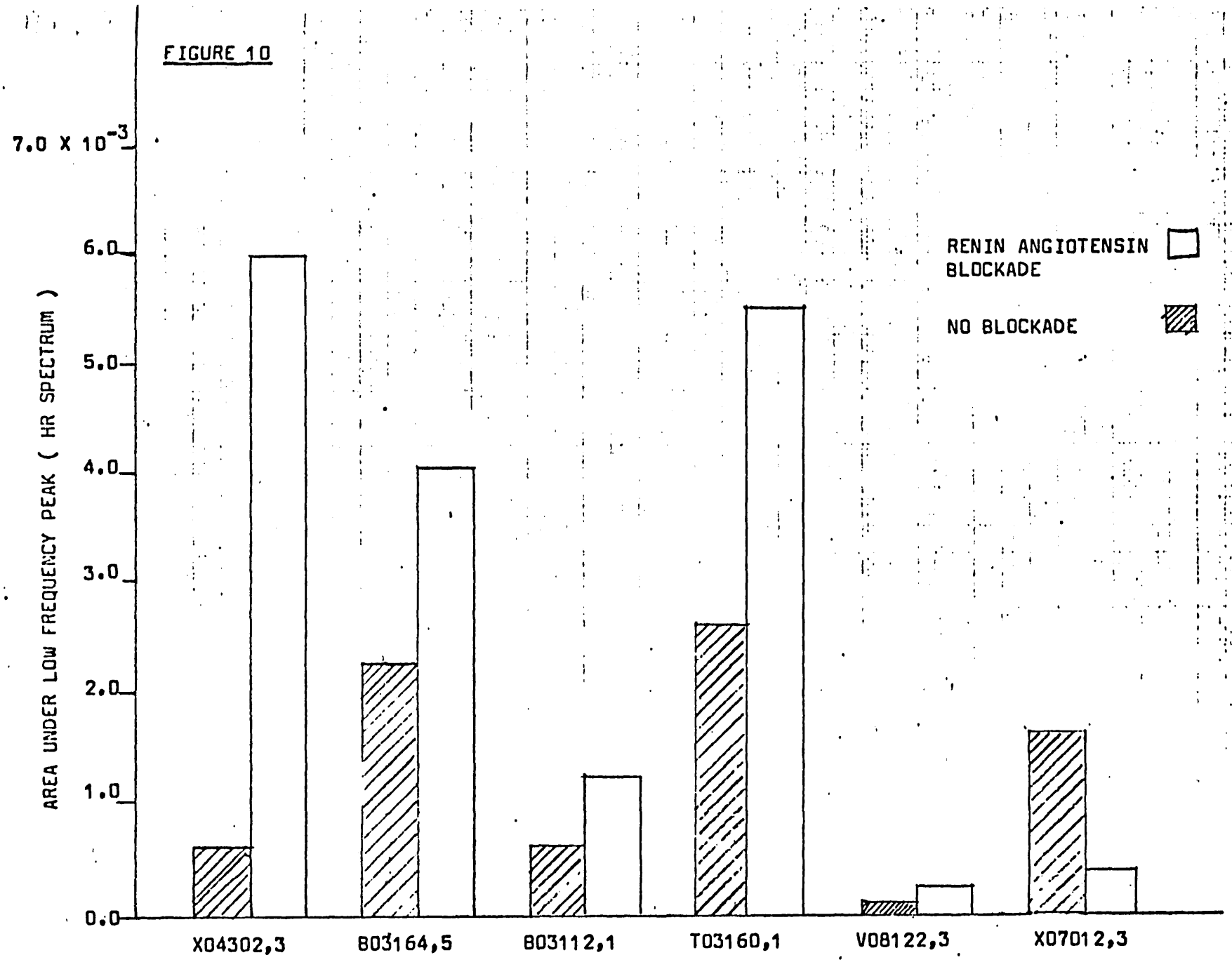

7.0 X 10⁻³
6.0
5.0
4.0
3.0
2.0
1.0
0.0
AREA UNDER LOW FREQUENCY PEAK (HR SPECTRUM)
RENIN ANGIOTENSIN BLOCKADE
NO BLOCKADE
X04302,3
B03164,5
B03112,1
T03160,1
V08122,3
X07012,3

FIGURE 11

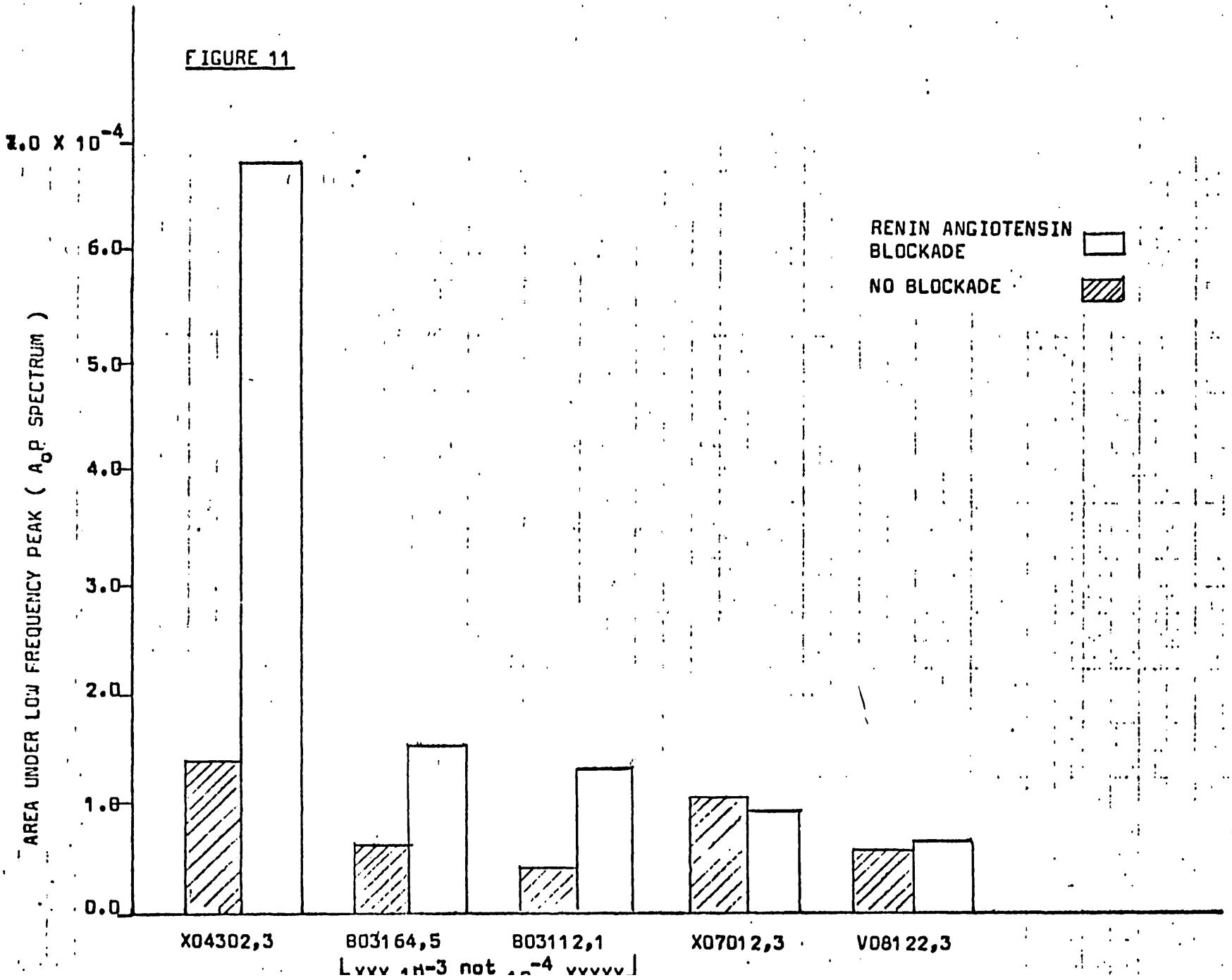

7.0 X 10⁻⁴
6.0
5.0
4.0
3.0
2.0
1.0
0.0
AREA UNDER LOW FREQUENCY PEAK (A0P SPECTRUM)
RENIN ANGIOTENSIN BLOCKADE
NO BLOCKADE
X04302,3
B03164,5
B03112,1
X07012,3
V08122,3

FIGURE 12

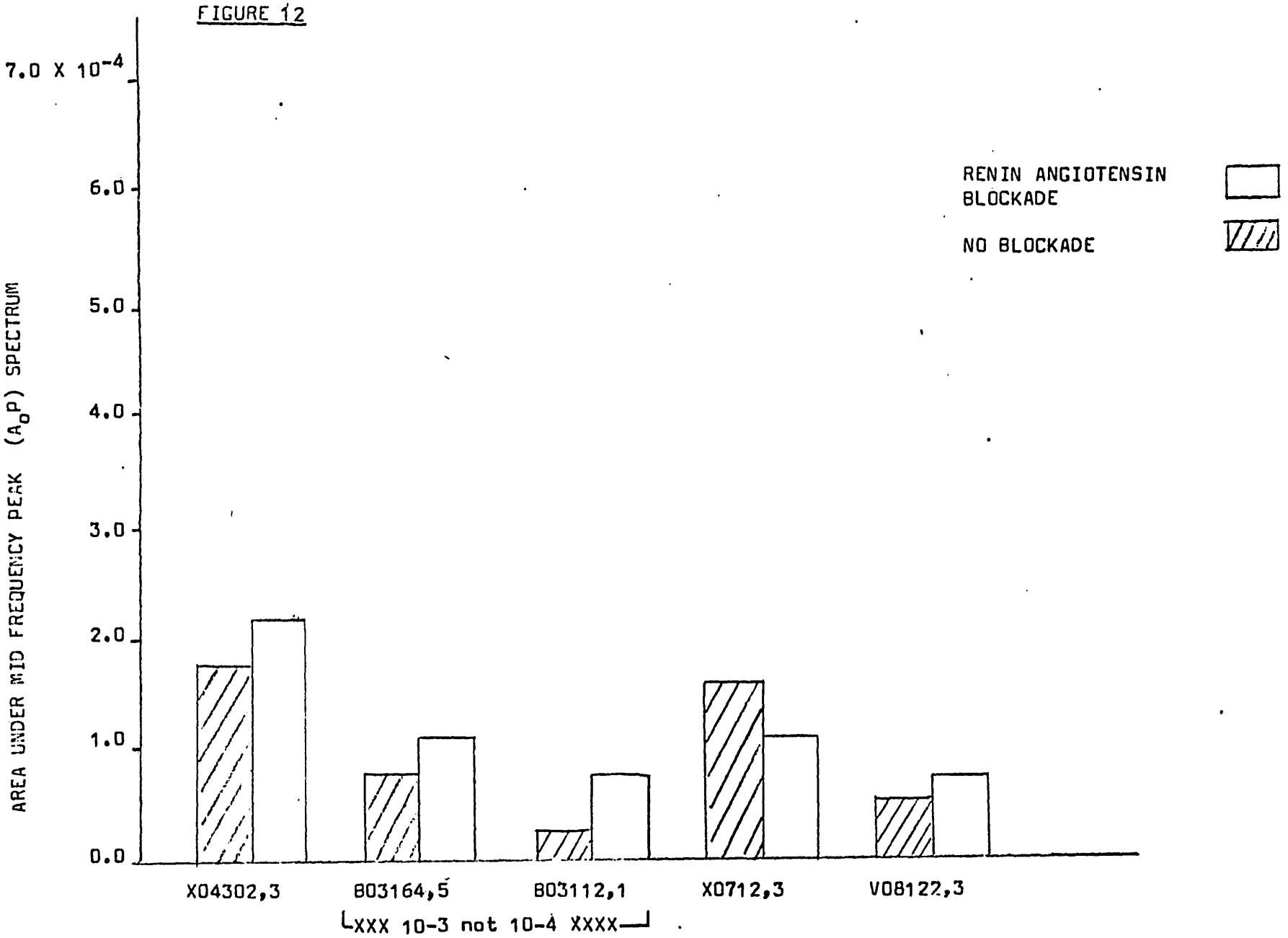
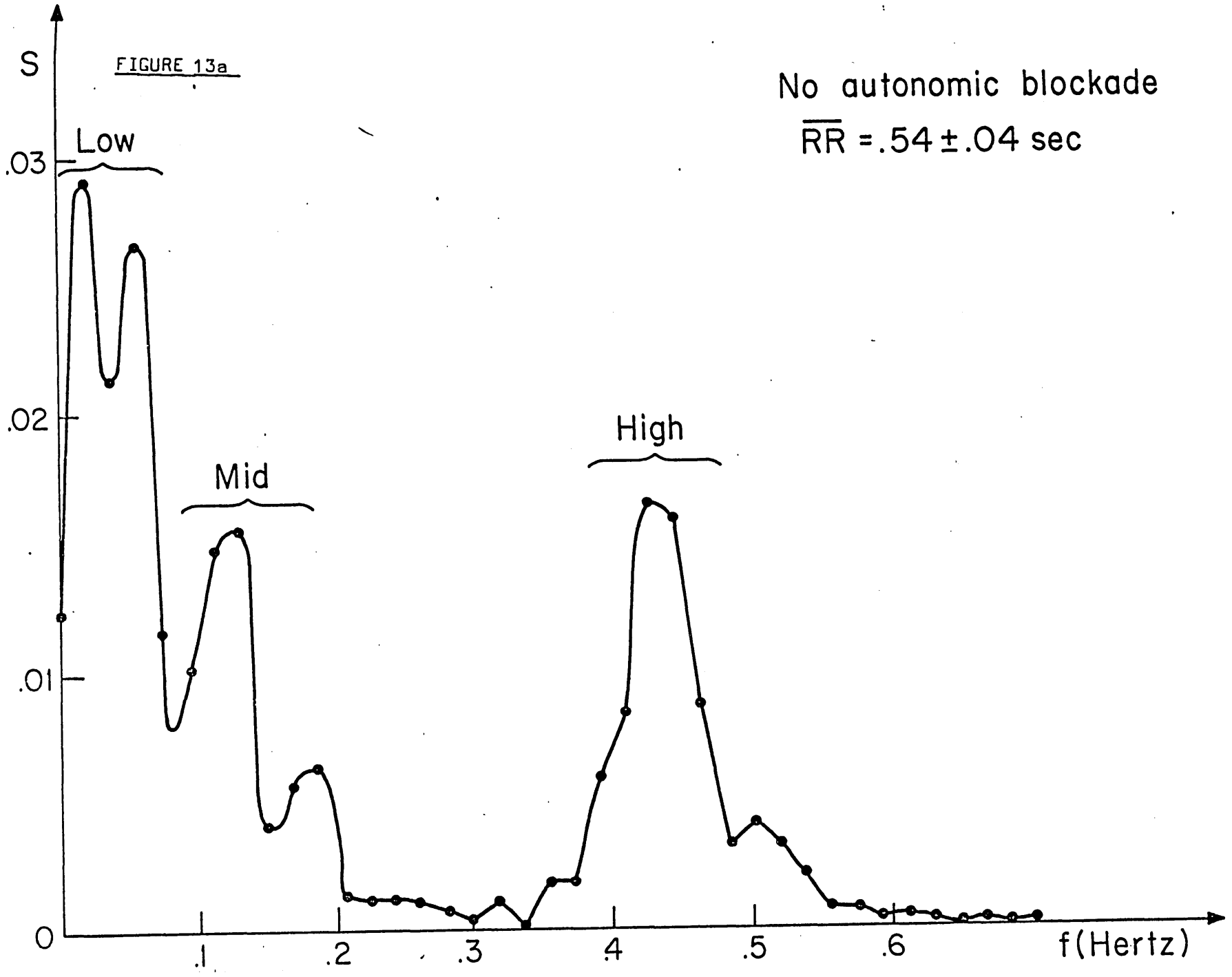

7.0 X 10-4
6.0
5.0
4.0
3.0
2.0
1.0
0.0
AREA UNDER MID FREQUENCY PEAK (AoP) SPECTRUM
RENIN ANGIOTENSIN BLOCKADE
NO BLOCKADE
X04302,3
B03164,5
B03112,1
X0712,3
V08122,3
XXX 10-3 not 10-4 XXXX

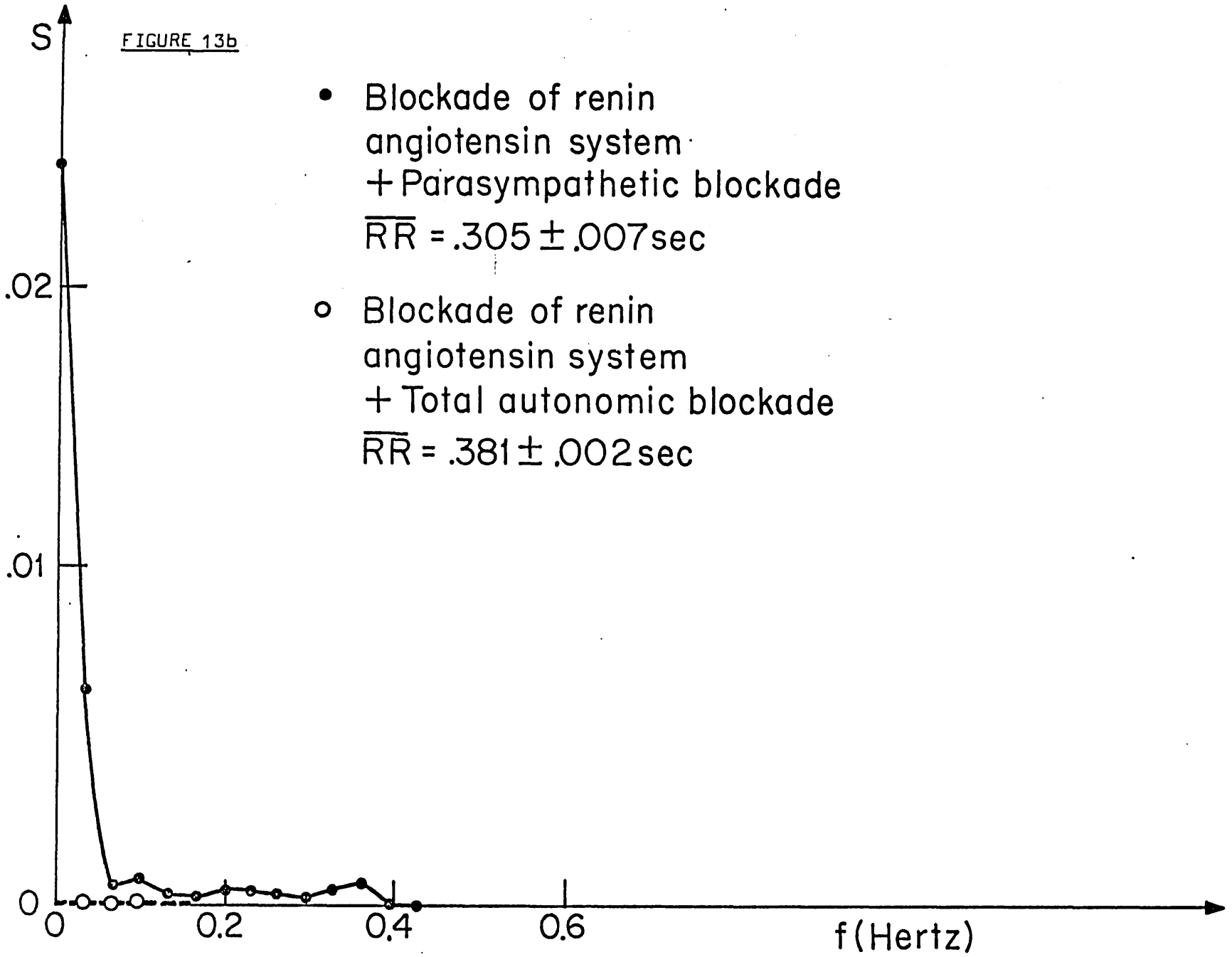
FIGURE 13a



No autonomic blockade

$\overline{RR}$ = .54 ± .04 sec

FIGURE 13b



- Blockade of renin angiotensin system + Parasympathetic blockade
  $\overline{RR}$ = .305 ± .007 sec
- Blockade of renin angiotensin system + Total autonomic blockade
  $\overline{RR}$ = .381 ± .002 sec

FIGURE 13c

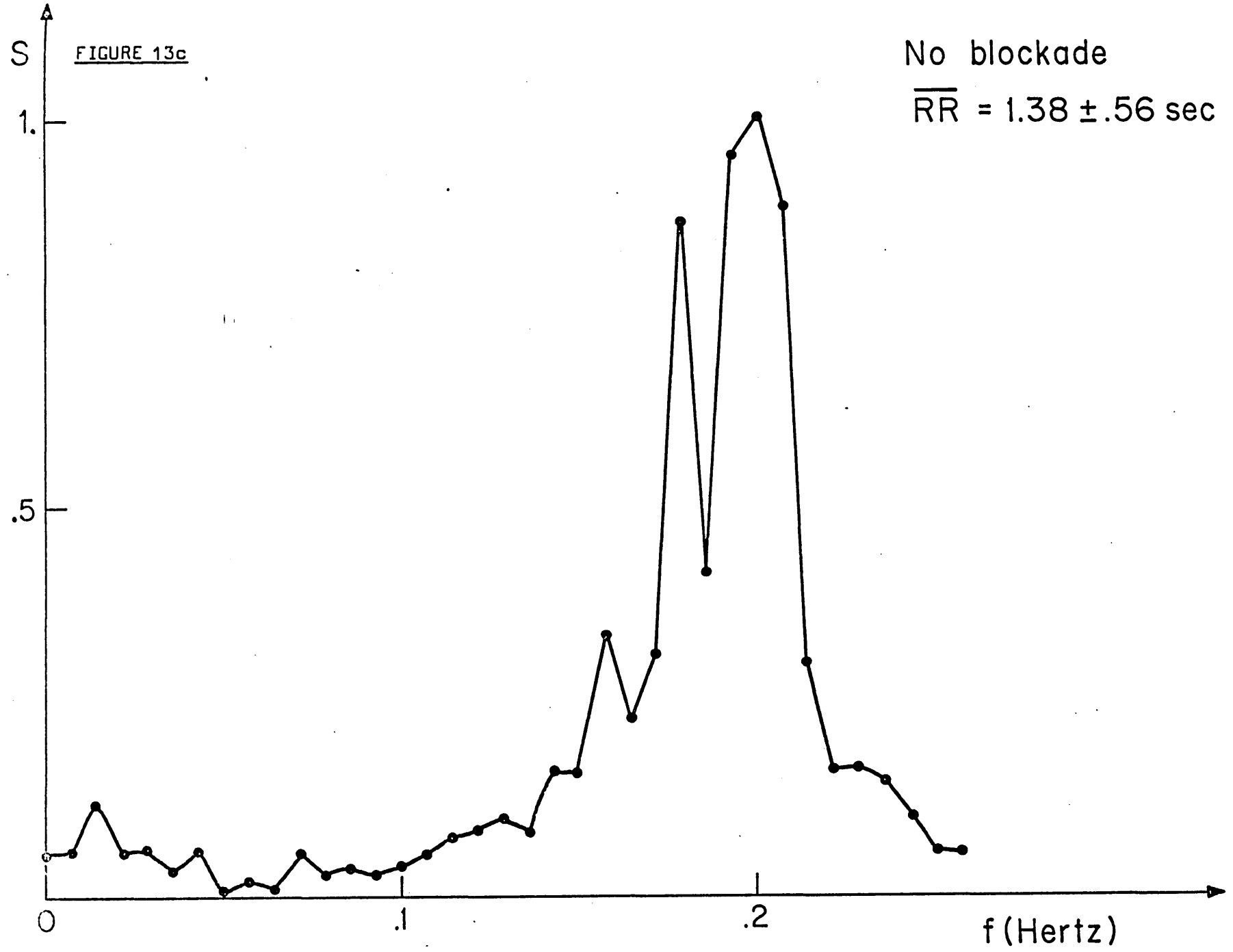
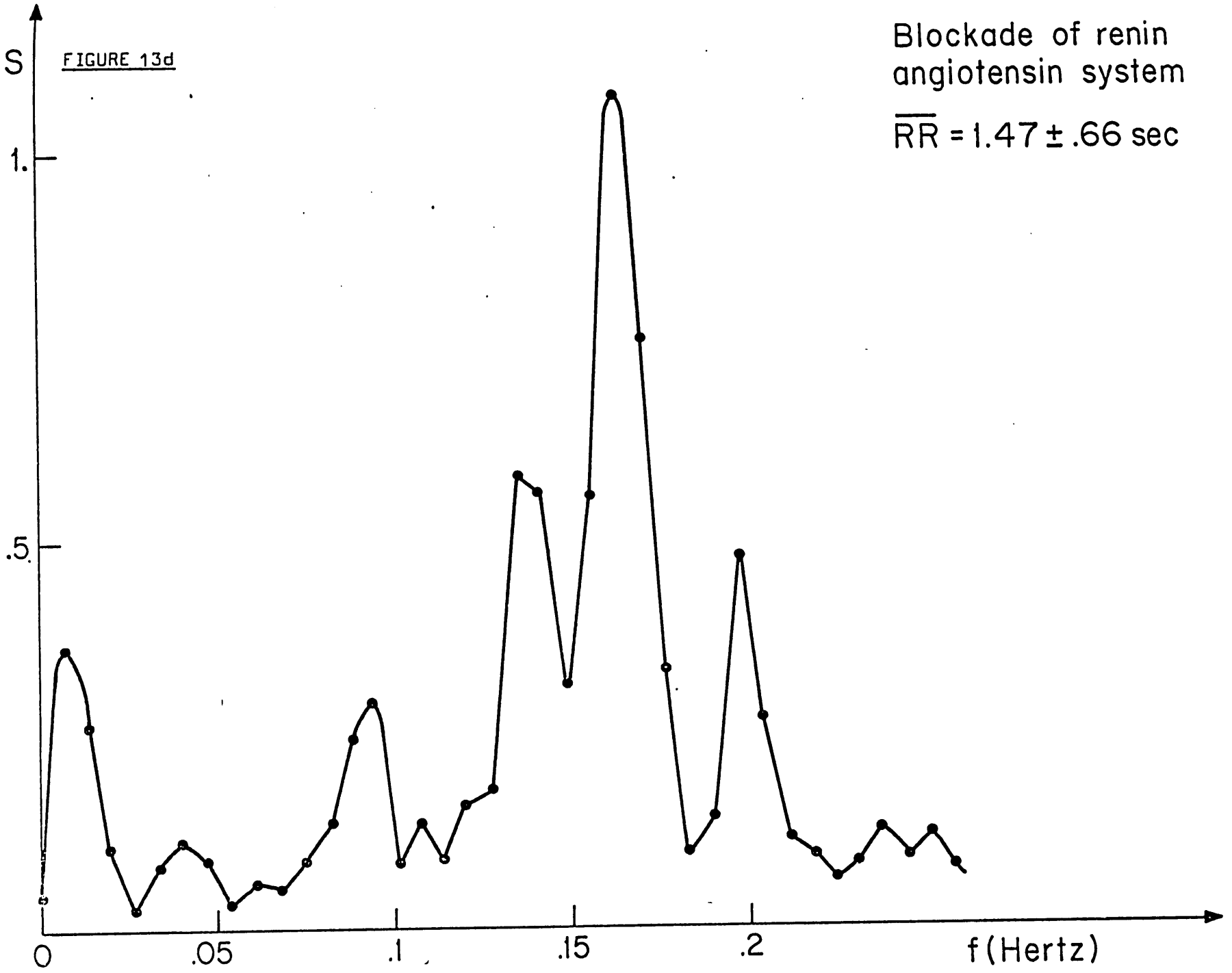


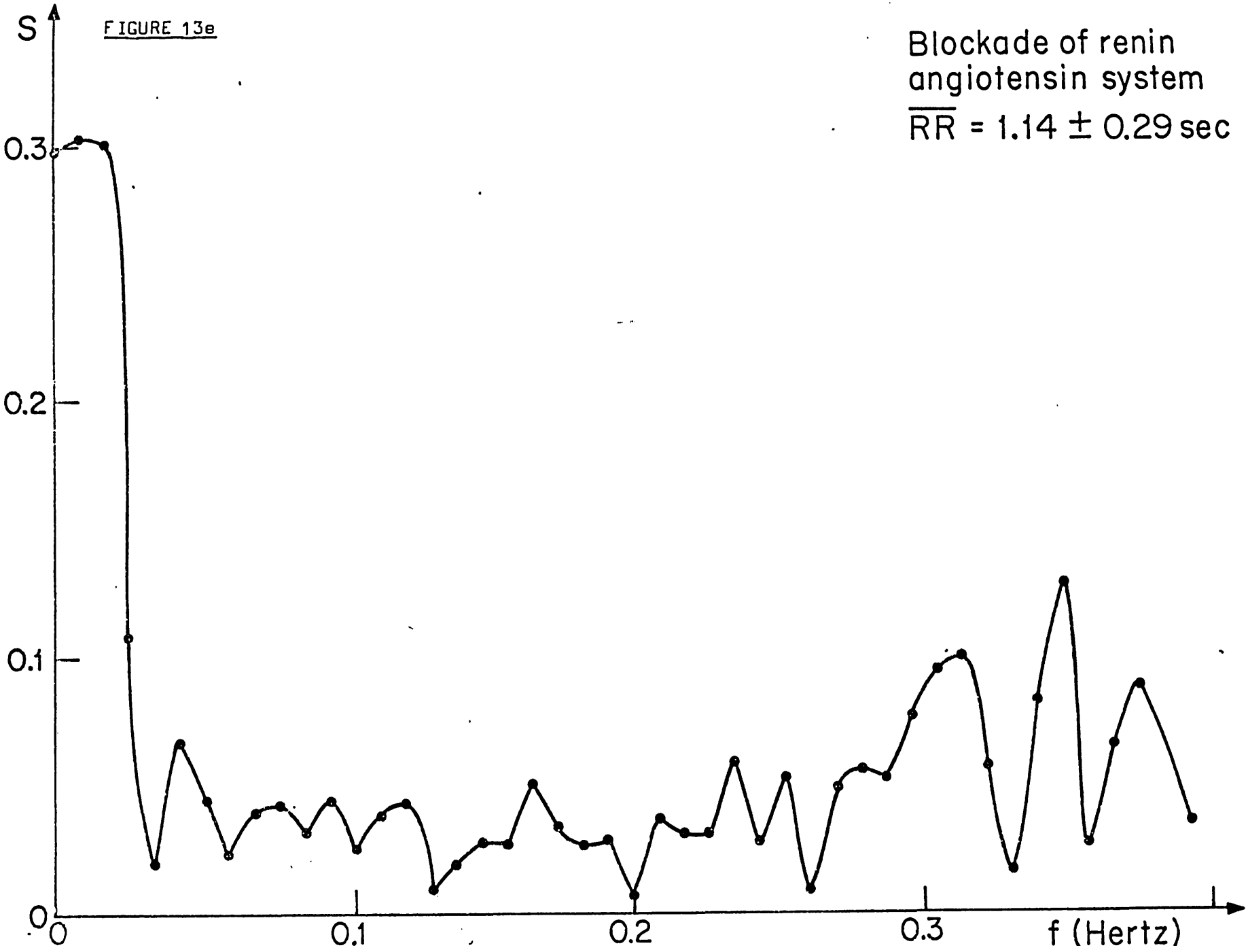
FIGURE 13d



Blockade of renin angiotensin system

$\overline{RR} = 1.47 \pm .66$ sec

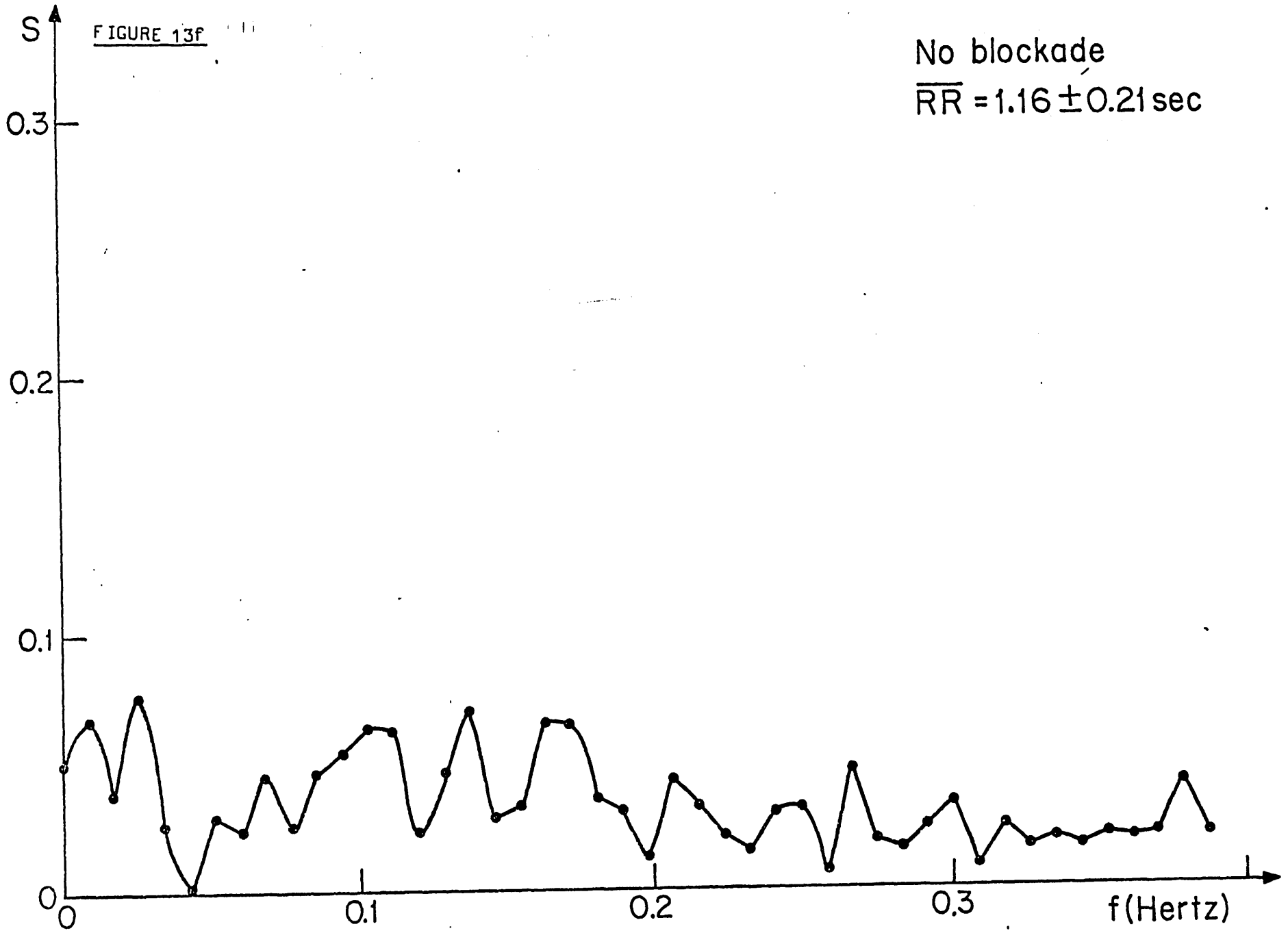
FIGURE 13e



Blockade of renin angiotensin system

$\overline{RR}$ = 1.14 ± 0.29 sec

FIGURE 13f


S
0.3
0.2
0.1
0
0
0.1
0.2
0.3
f(Hertz)
No blockade
$\overline{RR}$ = 1.16 ± 0.21 sec

DOG: BOHR

DATE OF EXPERIMENT: March 11,1980

BASELINE

DRUG : NONE

INTERVENTION #1

DRUG: Converting Enzyme Inhibitor

INTERVENTION #2

DRUG

INTERVENTION #3

DRUG

INTEGRATED AREAS OF SPECTRAL PEAKS

RUN	CHANNEL ANALYZED	LOW FREQ. PEAK	MID FREQ. PEAK	HIGH FREQ. PEAK
Baseline	HR	.68 E-3	1.32 E-3	1.65 E-4
	A_oP	.34 E-4	2.66 E-4	2.30 E-3
	Resp	4.91 E-4	2.02 E-4	1.36 E-3
INT. #1	HR	1.24 E-3	1.75 E-3	1.41 E-3
	A_oP	1.33 E-3	5.51 E-4	1.28 E-3
	Resp	2.47 E-4	1.47 E-4	1.59 E-3
INT. #2				
INT. #3				

FIGURE 14.1

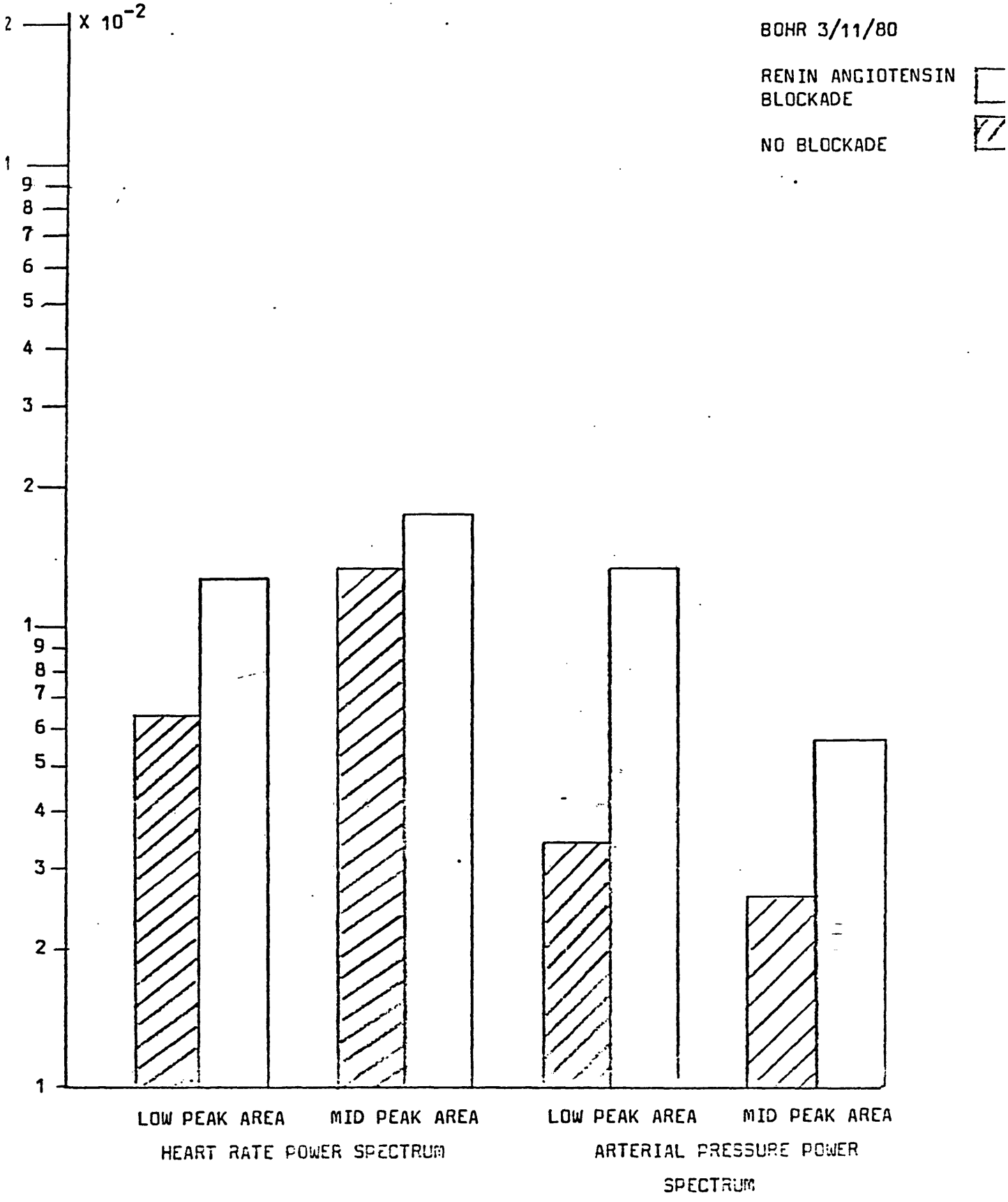
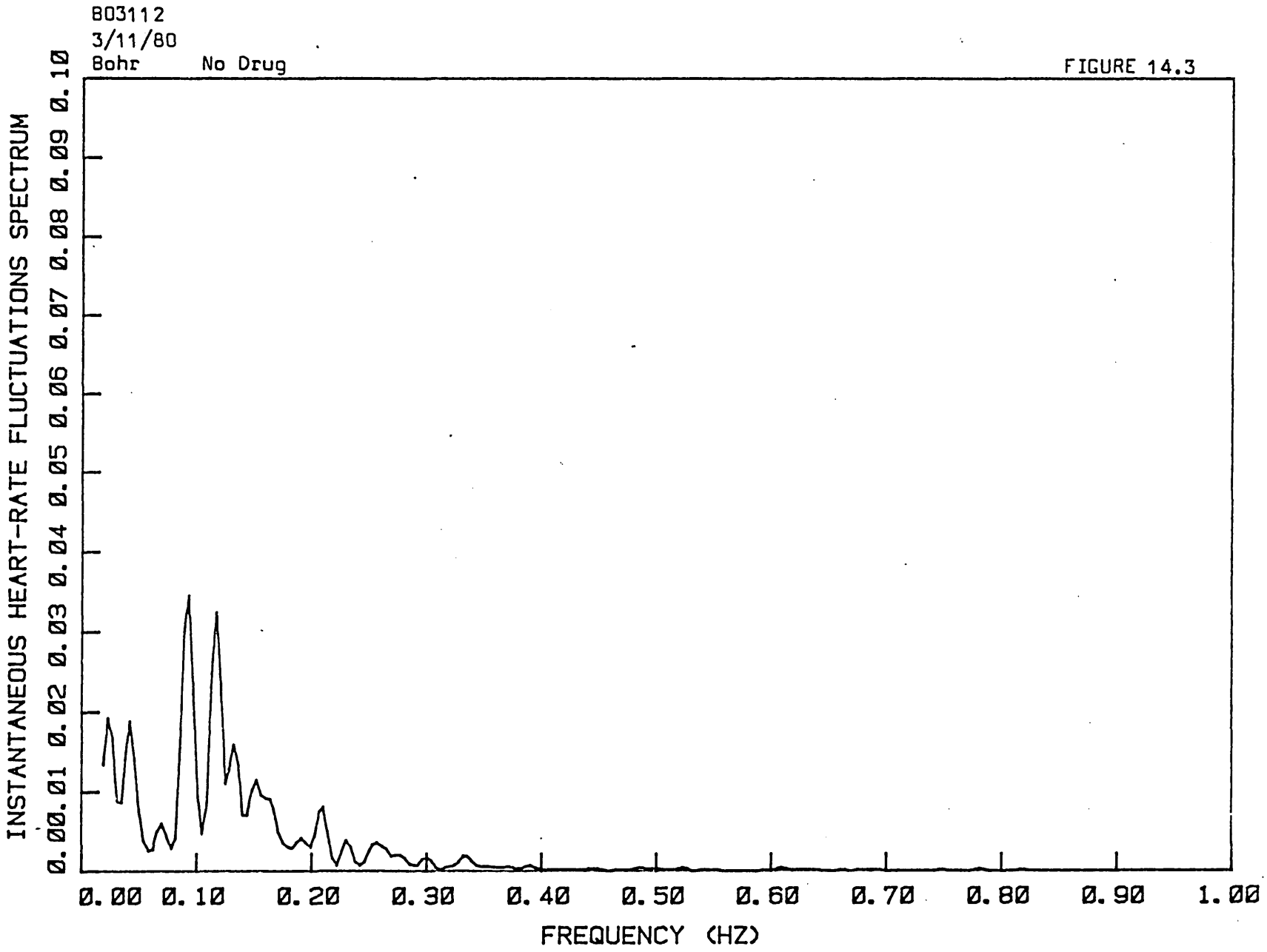
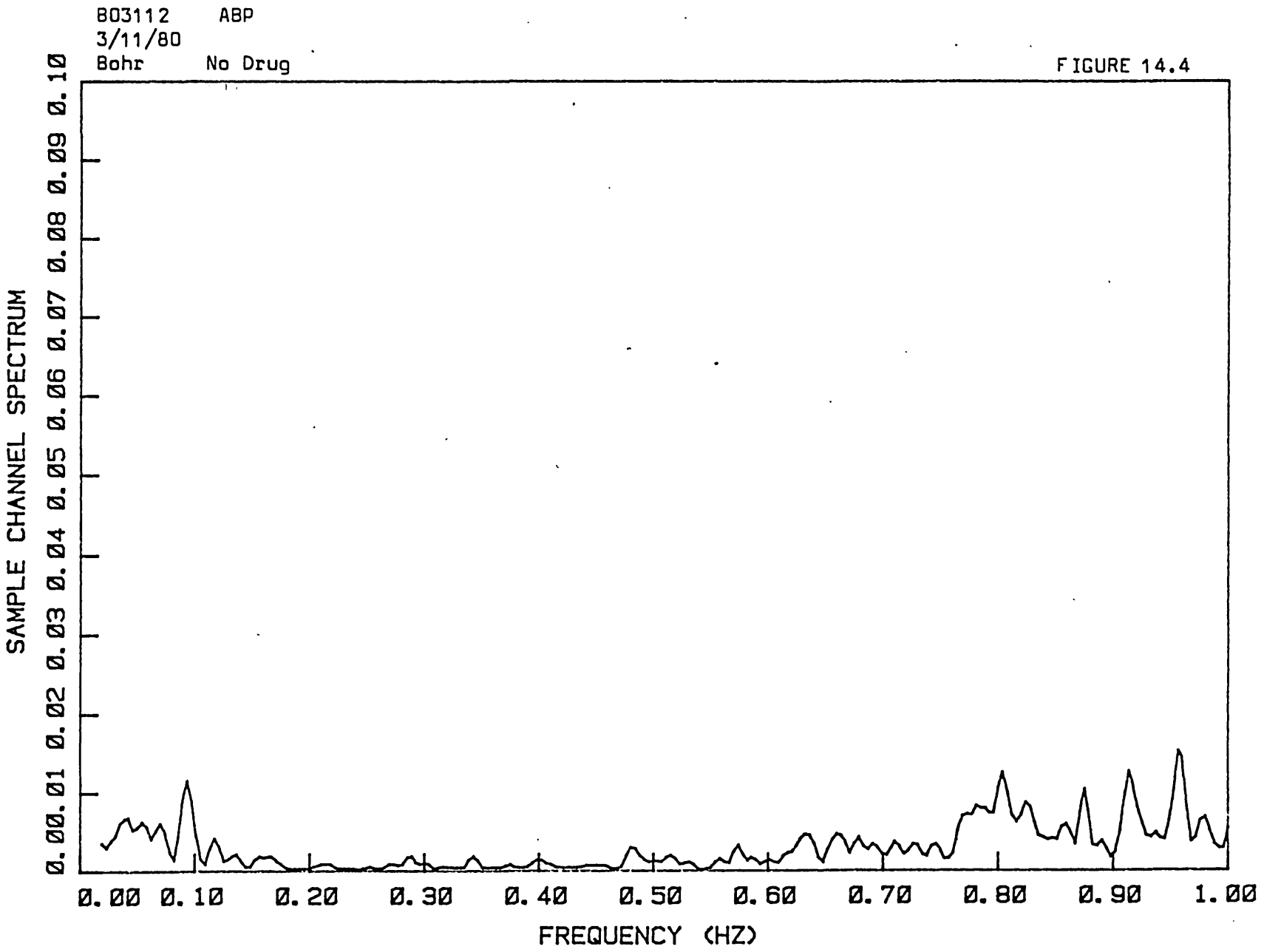
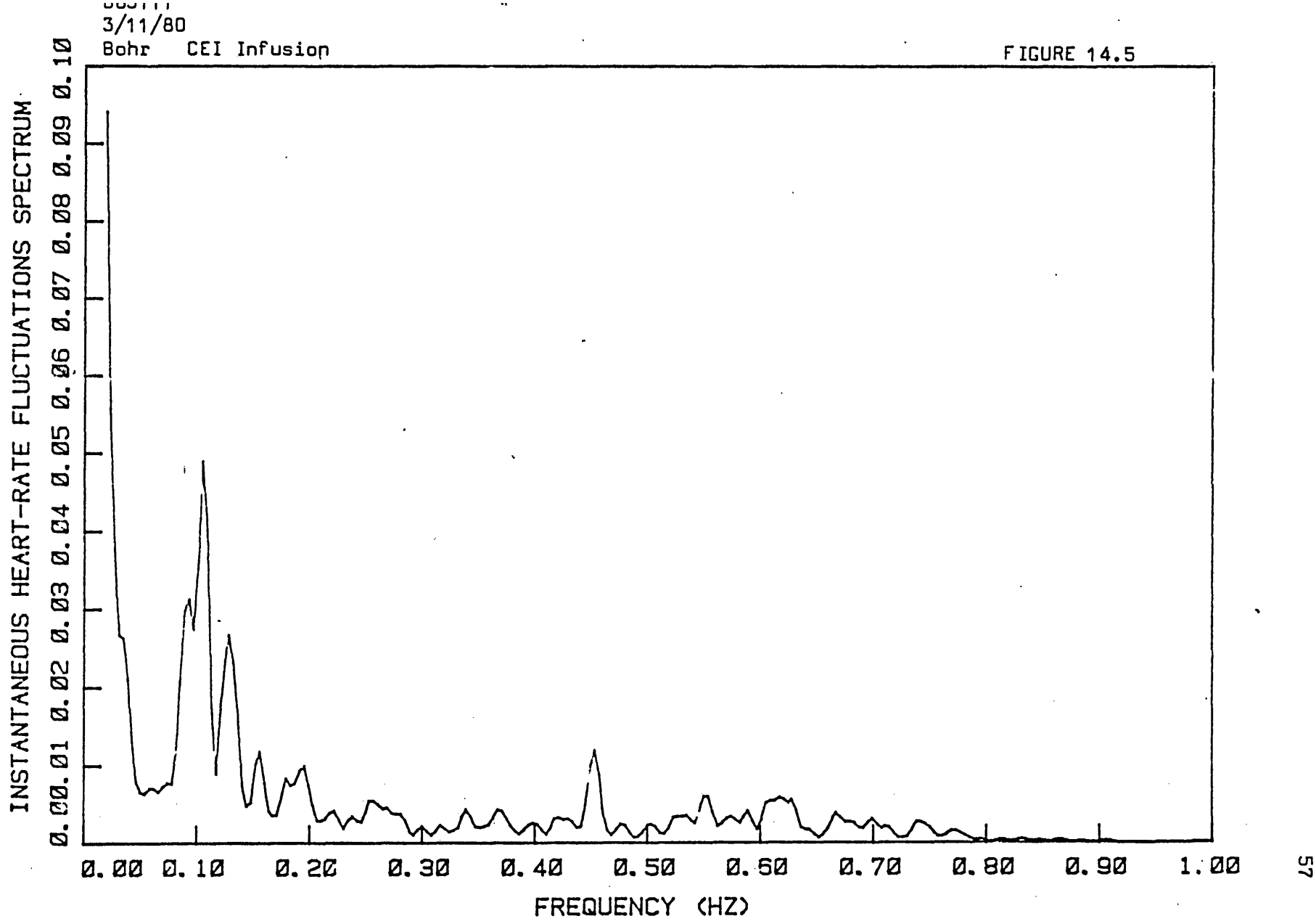
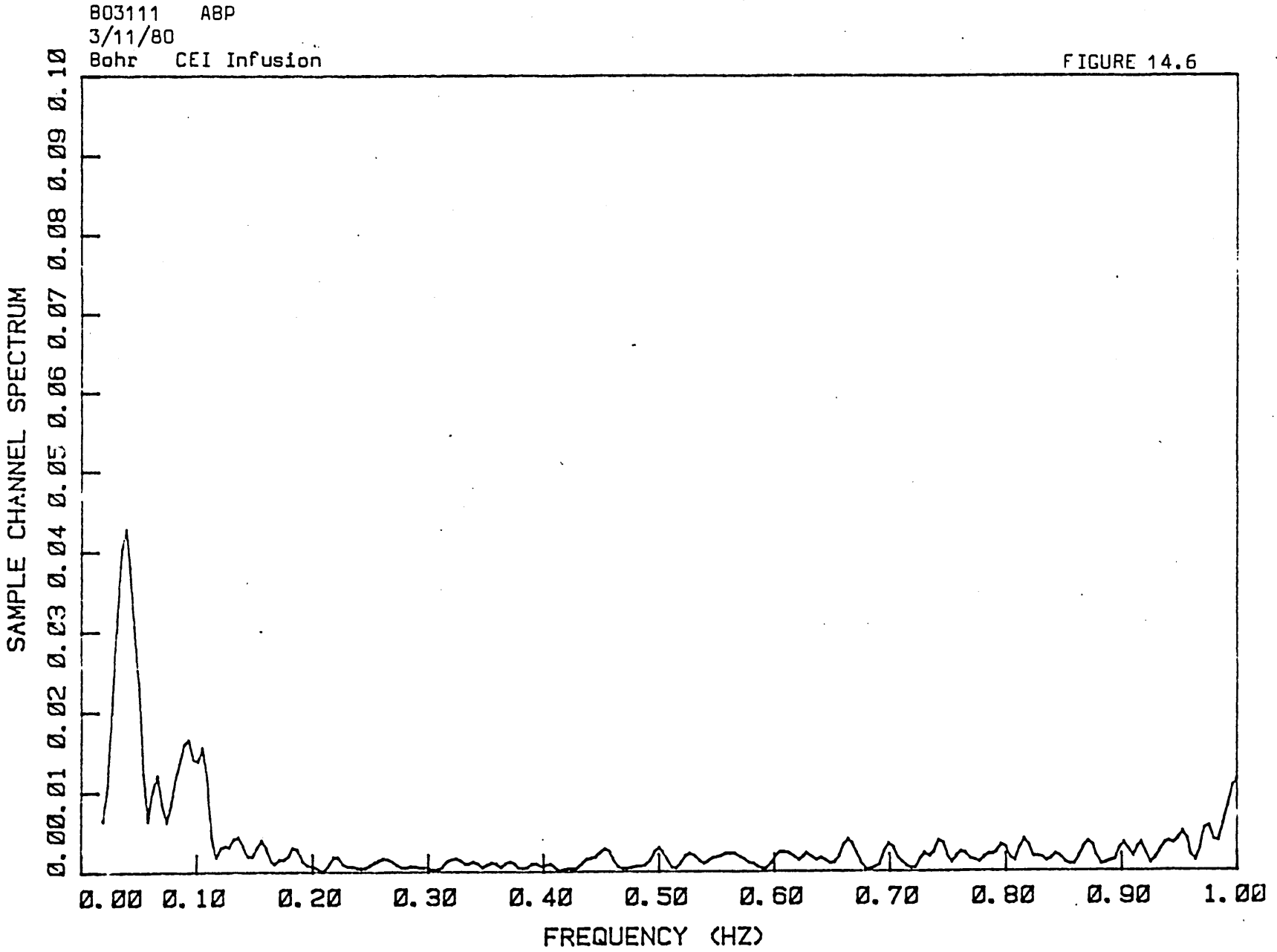

X 10^{-2}
2
1
9
8
7
6
5
4
3
2
1
9
8
7
6
5
4
3
2
1
BOHR 3/11/80
RENIN ANGIOTENSIN BLOCKADE
NO BLOCKADE
LOW PEAK AREA
MID PEAK AREA
LOW PEAK AREA
MID PEAK AREA
HEART RATE POWER SPECTRUM
ARTERIAL PRESSURE POWER SPECTRUM

FIGURE 14.2


B03112
3/11/80
Bohr No Drug
FIGURE 14.3
INSTANTANEOUS HEART-RATE FLUCTUATIONS SPECTRUM
0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.10
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)


B03112 ABP
3/11/80
Bohr No Drug
FIGURE 14.4
SAMPLE CHANNEL SPECTRUM
0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.10
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)


3/11/80
Bohr CEI Infusion
FIGURE 14.5
INSTANTANEOUS HEART-RATE FLUCTUATIONS SPECTRUM
0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.10
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)


B03111 ABP
3/11/80
Bohr CEI Infusion
FIGURE 14.6
SAMPLE CHANNEL SPECTRUM
0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.10
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)

DOG: BOHR

DATE OF EXPERIMENT: March 16,1980

BASELINE

DRUG : NONE

INTERVENTION #1

DRUG : Converting Enzyme Inhibitor

INTERVENTION #2

INTERVENTION #3

DRUG

INTEGRATED AREAS OF SPECTRAL PEAKS

RUN	CHANNEL ANALYZED	LOW FREQ. PEAK	MID FREQ. PEAK	HIGH FREQ. PEAK
Baseline	HR	2.24 E-3	6.67 E-3	4.07 E-3
	A_oP	0.62 E-3	0.74 E-3	7.72 E-3
	Resp	6.72 E-3	3.62 E-3	1.82 E-3
INT. #1	HR	4.04 E-3	4.27 E-3	2.29 E-3
	A_oP	1.50 E-3	1.02 E-3	7.38 E-3
	Resp	3.65 E-3	1.70 E-3	0.60 E-3
INT. #2				
INT. #3				

FIGURE 15.1

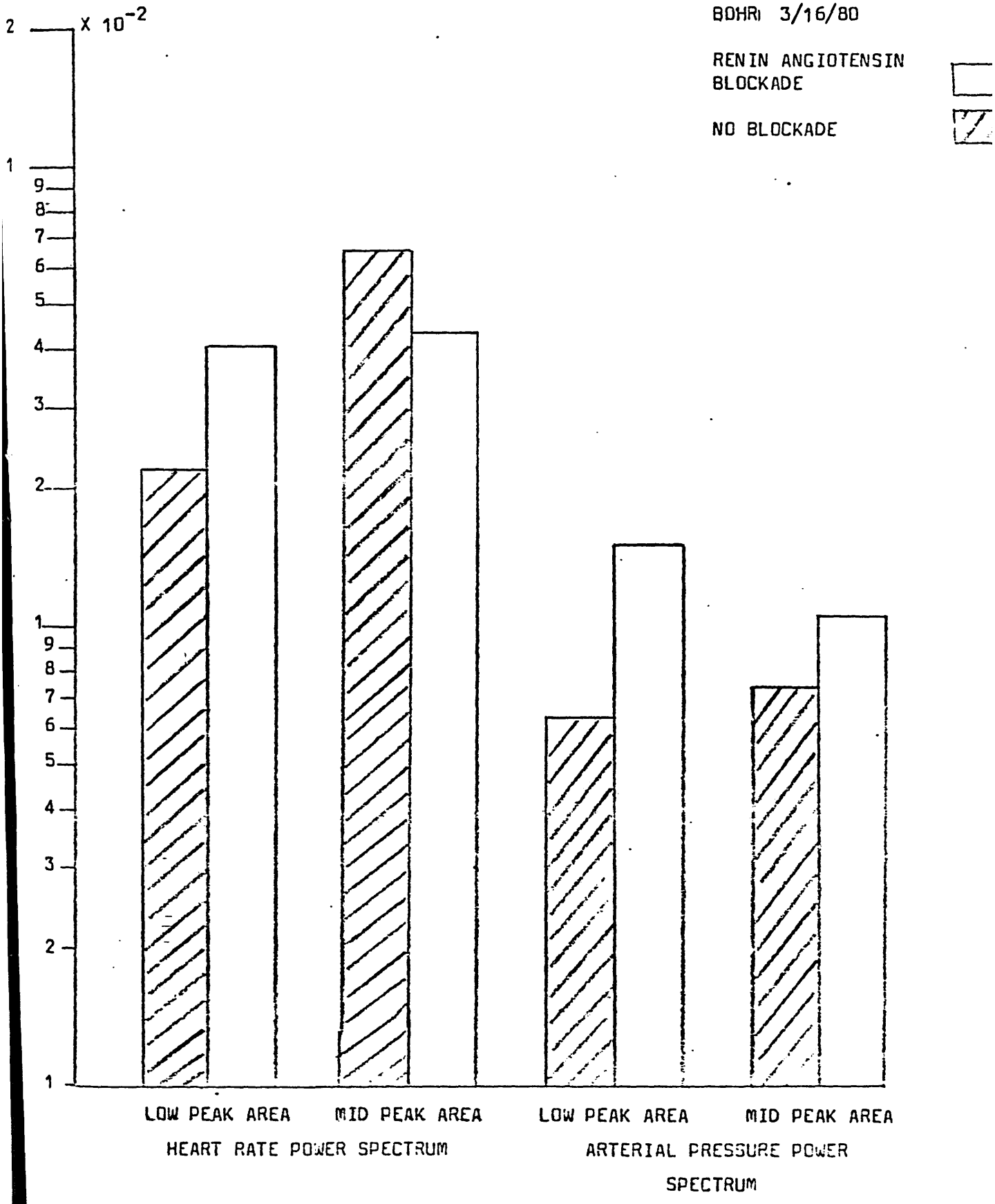
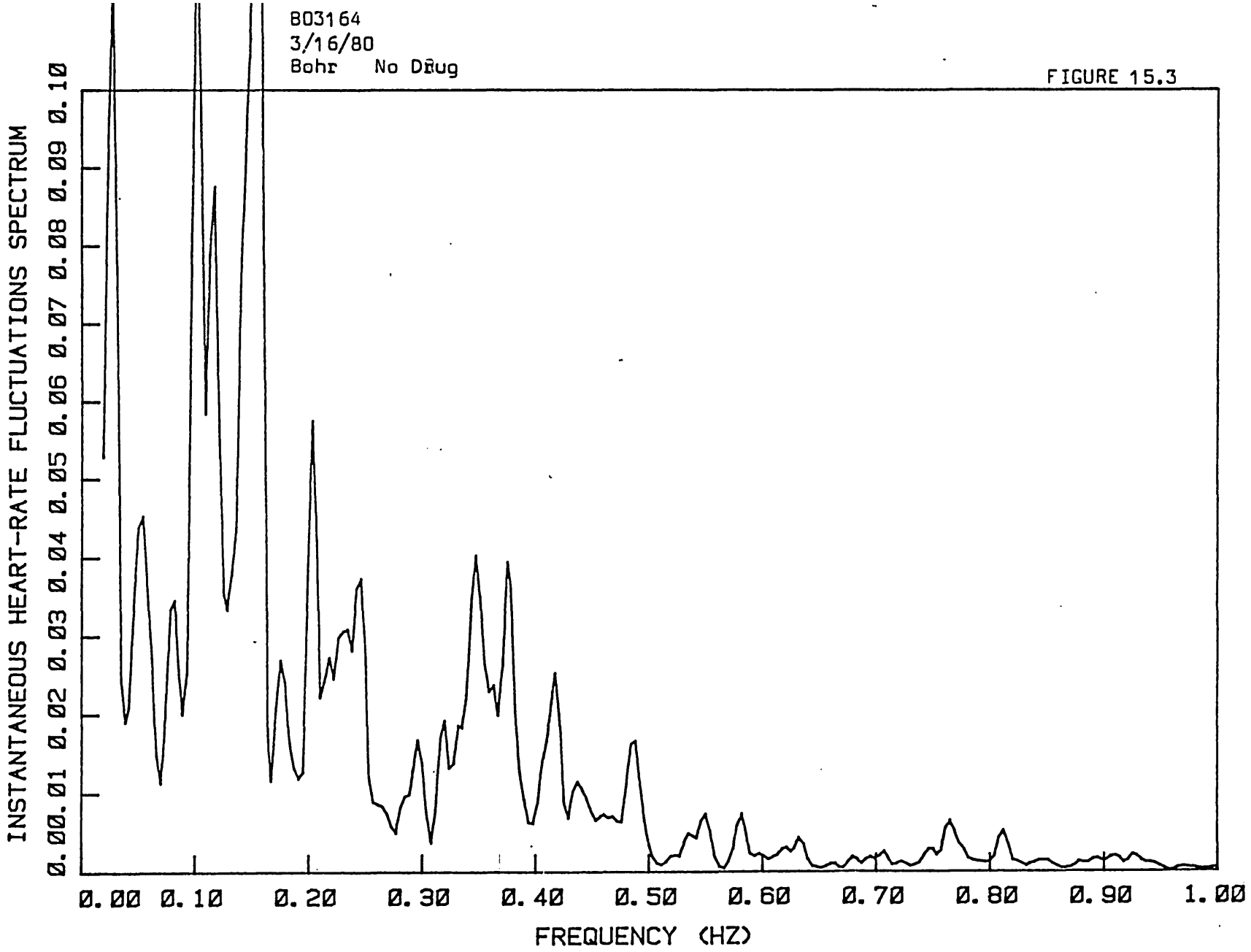
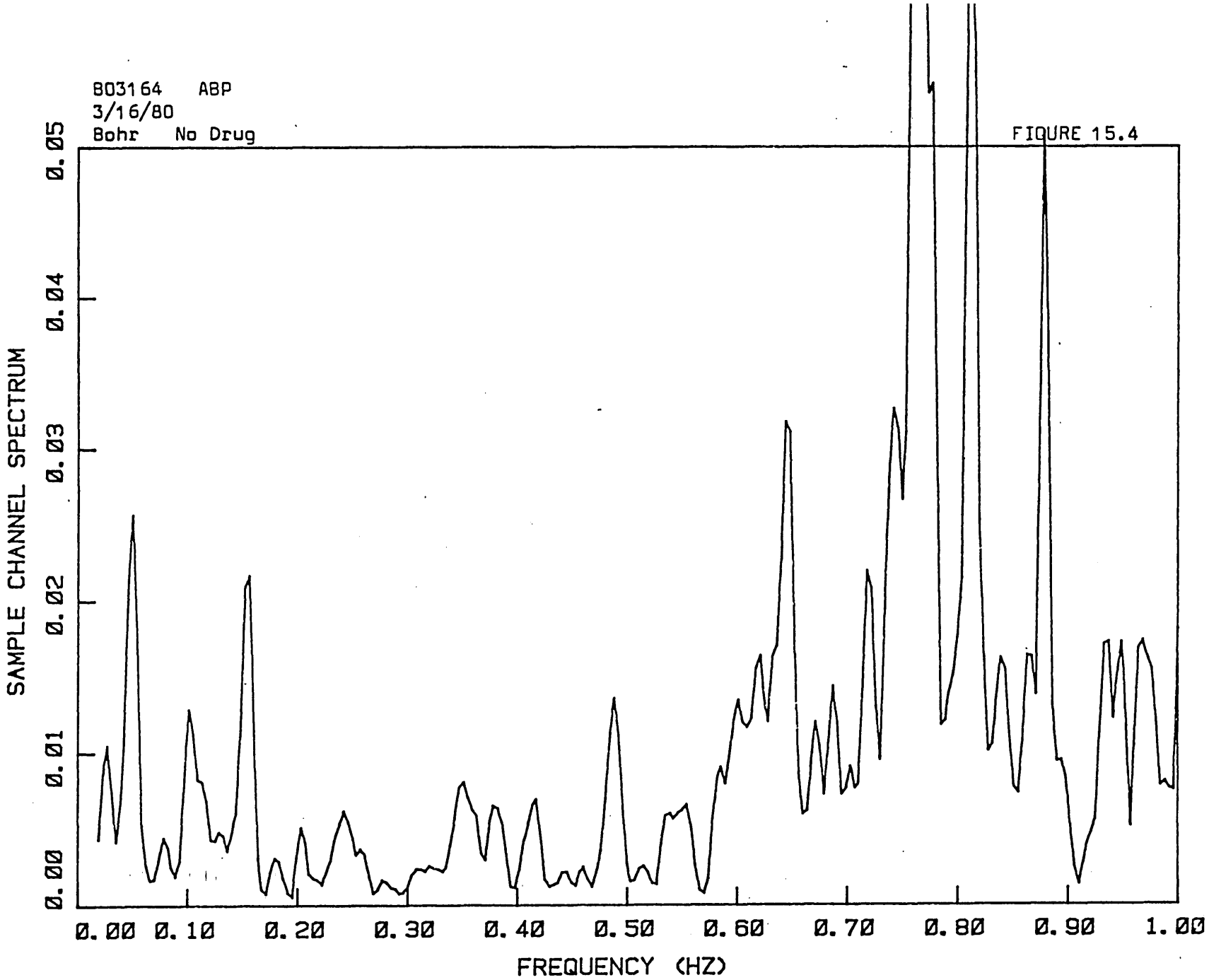
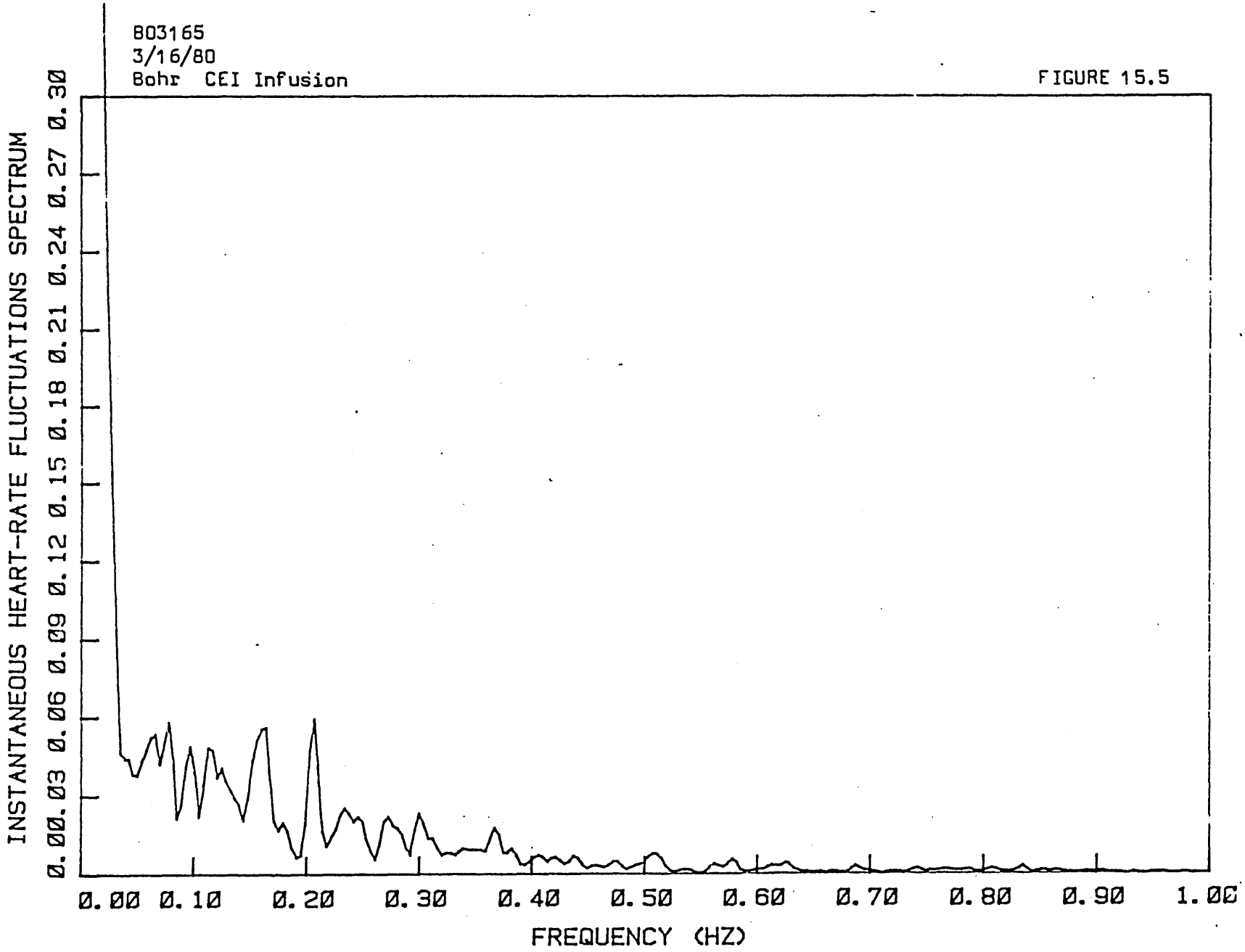
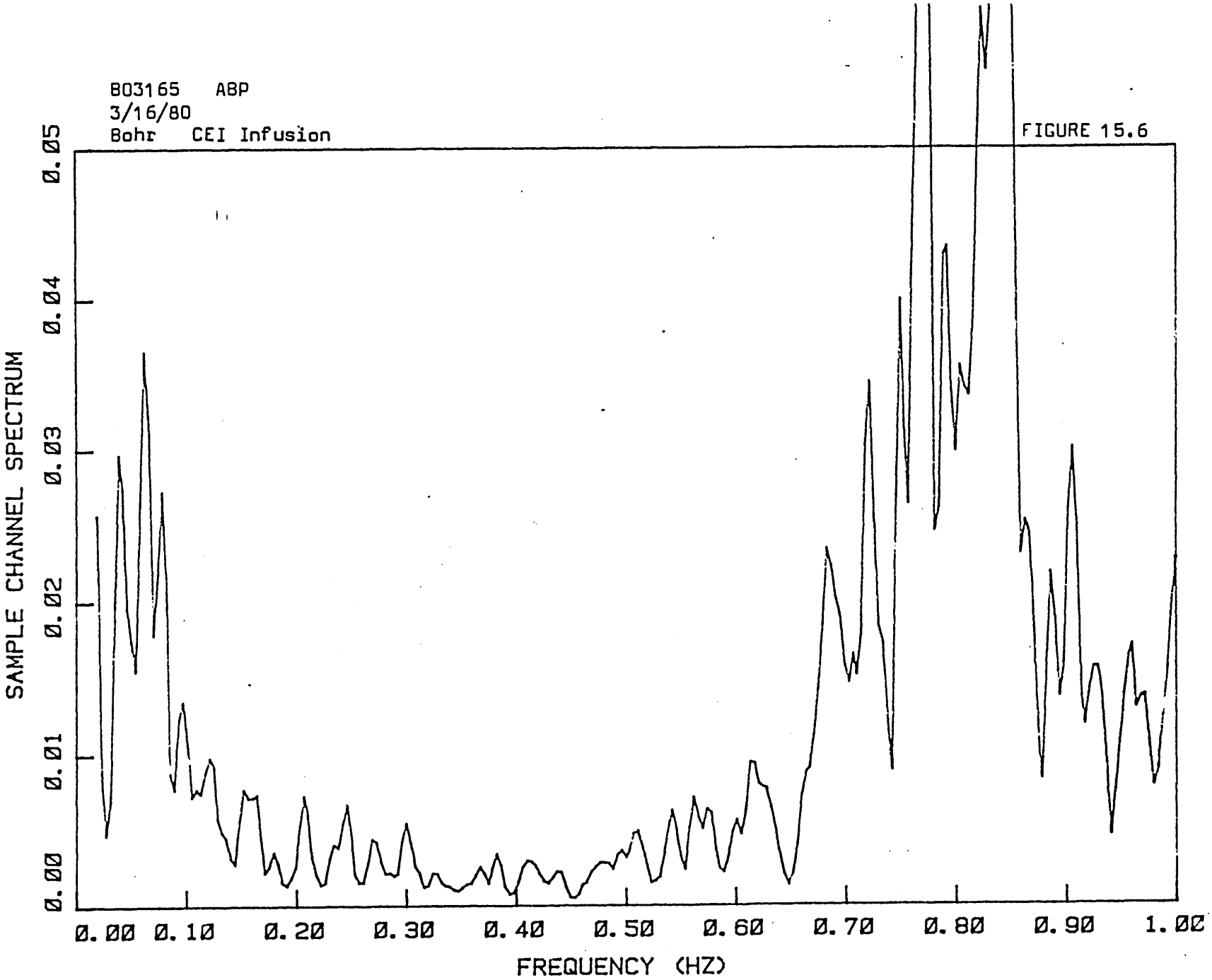

X 10^{-2}
2
1
9
8
7
6
5
4
3
2
1
9
8
7
6
5
4
3
2
1
BDHR 3/16/80
RENIN ANGIOTENSIN BLOCKADE
NO BLOCKADE
LOW PEAK AREA
MID PEAK AREA
LOW PEAK AREA
MID PEAK AREA
HEART RATE POWER SPECTRUM
ARTERIAL PRESSURE POWER SPECTRUM

FIGURE 15.2


B03164
3/16/80
Bohr No Drug
FIGURE 15.3
INSTANTANEOUS HEART-RATE FLUCTUATIONS SPECTRUM
0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.10
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)


B031 64 ABP
3/16/80
Bohr No Drug
FIQURE 15.4
SAMPLE CHANNEL SPECTRUM
0.05
0.04
0.03
0.02
0.01
0.00
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)


803165
3/16/80
Bohr CEI Infusion
FIGURE 15.5
INSTANTANEOUS HEART-RATE FLUCTUATIONS SPECTRUM
0.00 0.03 0.06 0.09 0.12 0.15 0.18 0.21 0.24 0.27 0.30
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)


B03165 ABP
3/16/80
Bohr CEI Infusion
FIGURE 15.6
SAMPLE CHANNEL SPECTRUM
0.05
0.04
0.03
0.02
0.01
0.00
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)

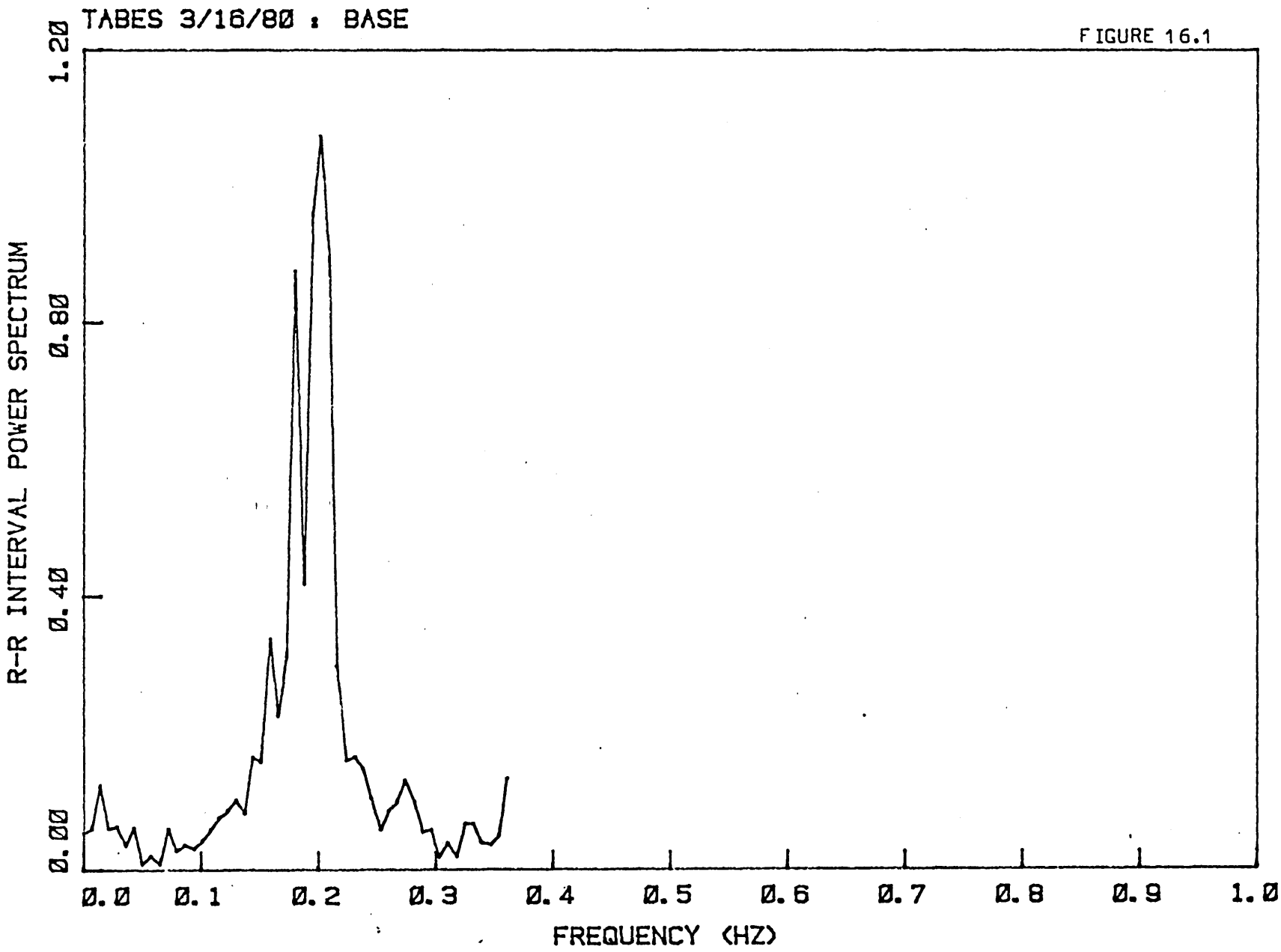
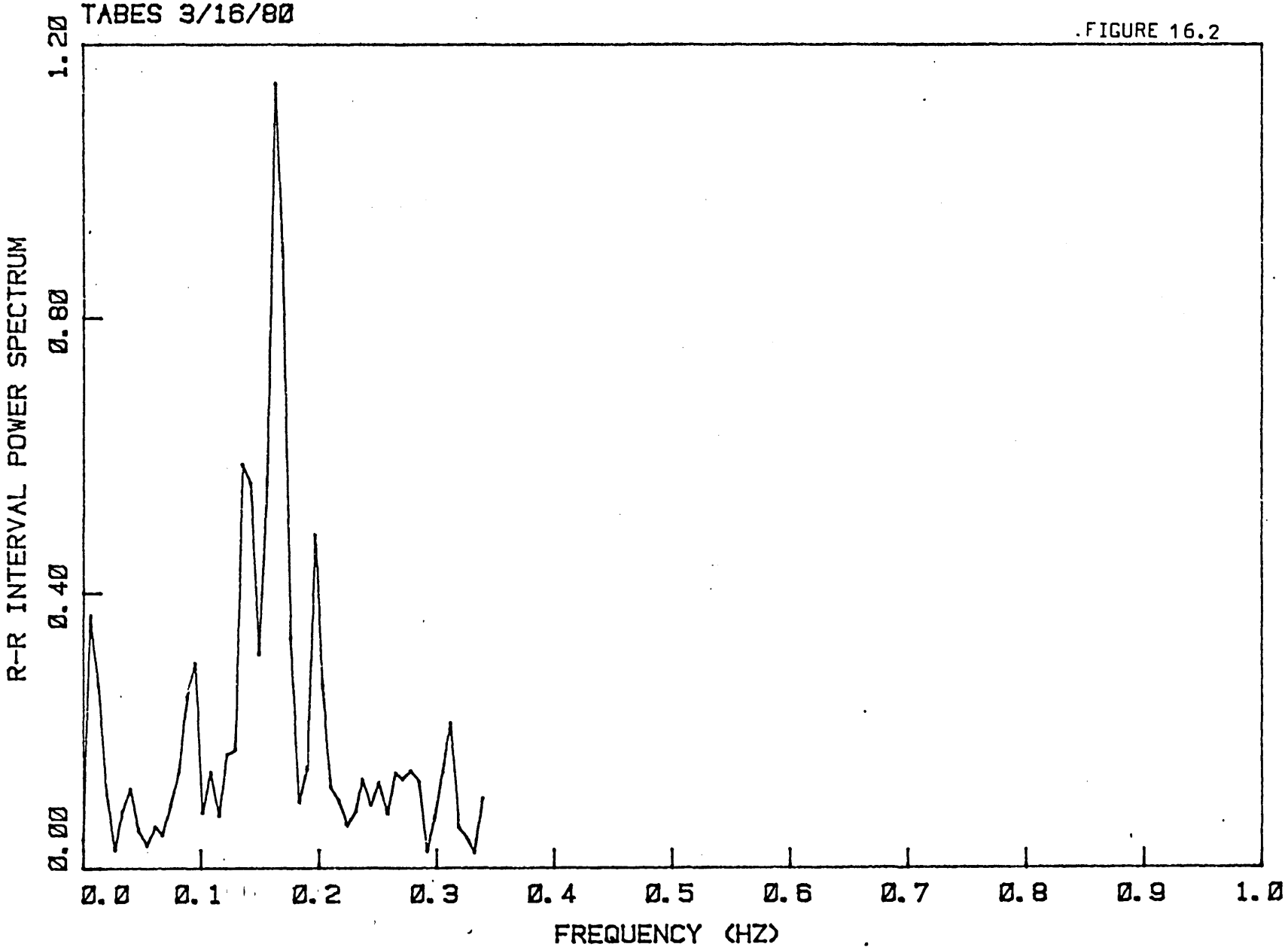

TABES 3/16/80 : BASE
R-R INTERVAL POWER SPECTRUM
1.20
0.80
0.40
0.00
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
FREQUENCY (HZ)

FIGURE 16.1


TABES 3/16/80
FIGURE 16.2
R-R INTERVAL POWER SPECTRUM
1.20
0.80
0.40
0.00
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
FREQUENCY (HZ)

DOG: XENON

DATE OF EXPERIMENT: April 30,1980

BASELINE

DRUG : NONE

INTERVENTION #1

DRUG: Converting Enzyme Inhibitor

INTERVENTION #2

DRUG

INTERVENTION #3

DRUG

INTEGRATED AREAS OF SPECTRAL PEAKS

RUN	CHANNEL ANALYZED	LOW FREQ. PEAK	MID FREQ. PEAK	HIGH FREQ. PEAK
Baseline	HR	6.61 E-4	2.1 E-2	--------
	A_oP	1.37 E-4	1.7 E-2	2.3 E-3
	Resp	2.28 E-3	4.6 E-4	1.31 E-2
INT. #1	HR	6.03 E-3	1.7 E-2	--------
	A_oP	6.8 E-4	2.15 E-3	1.3 E-3
	Resp	5.43 E-3	1.66 E-3	1.72 E-3
INT. #2				
INT. #3				

FIGURE 17.1

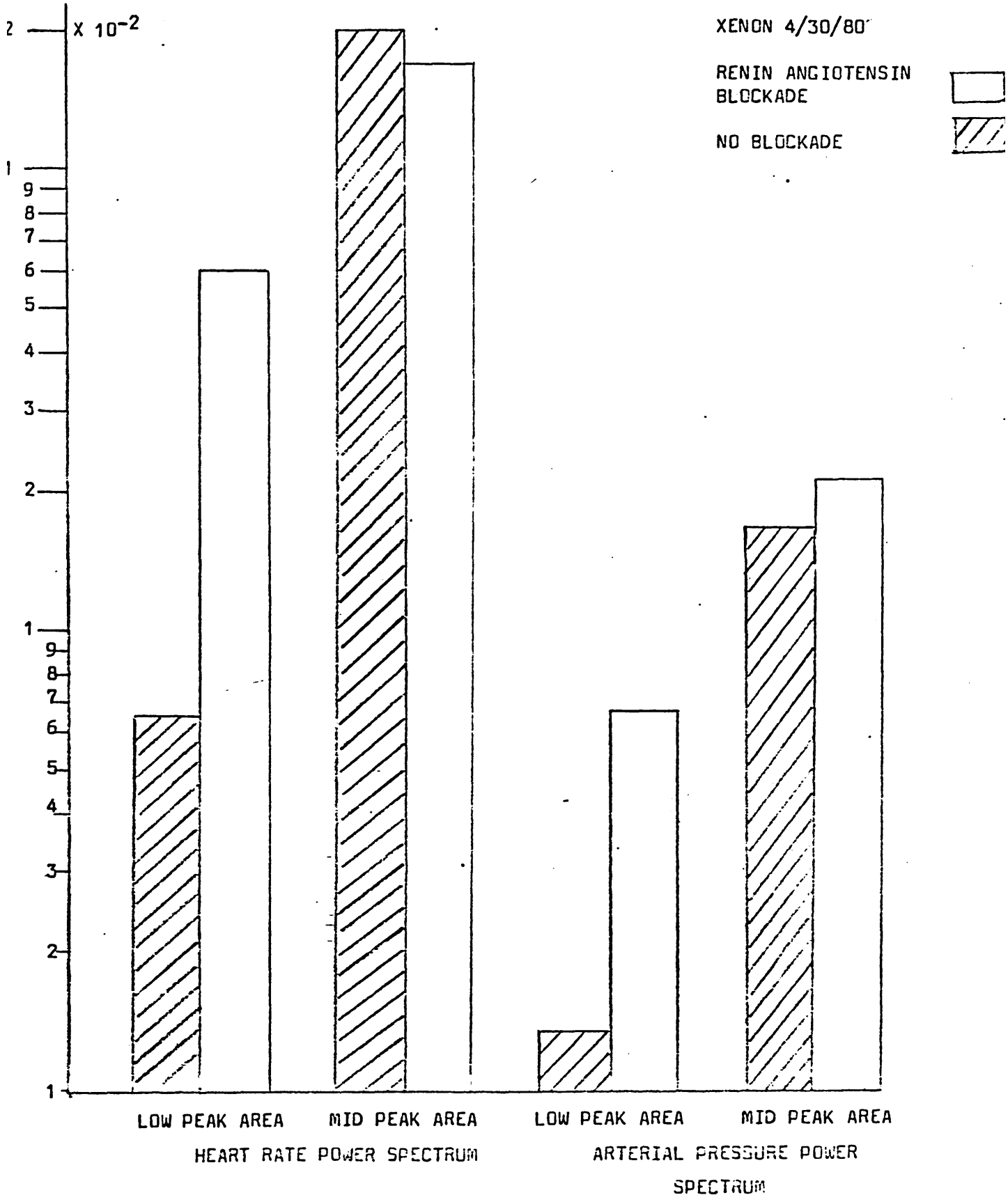
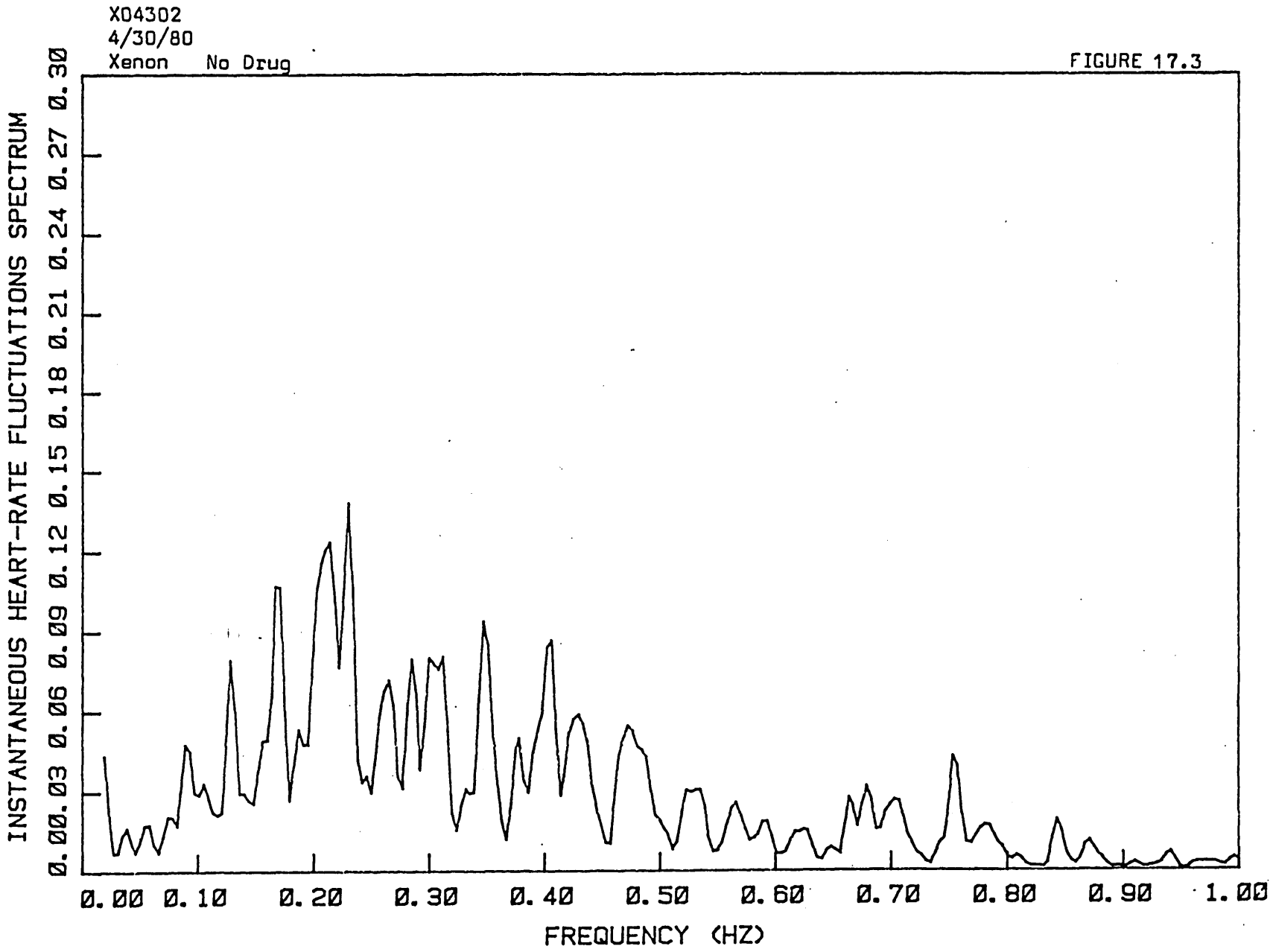
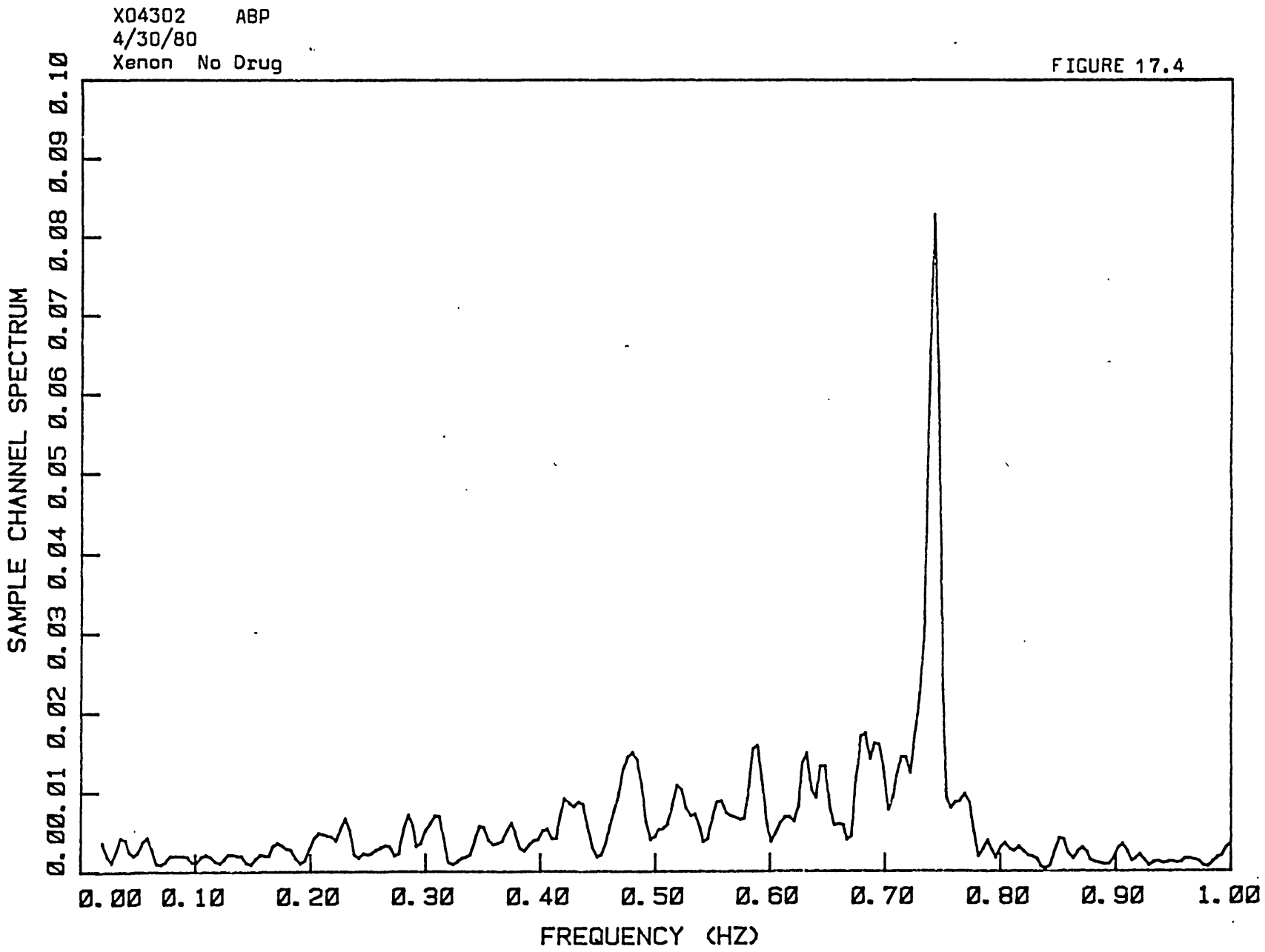
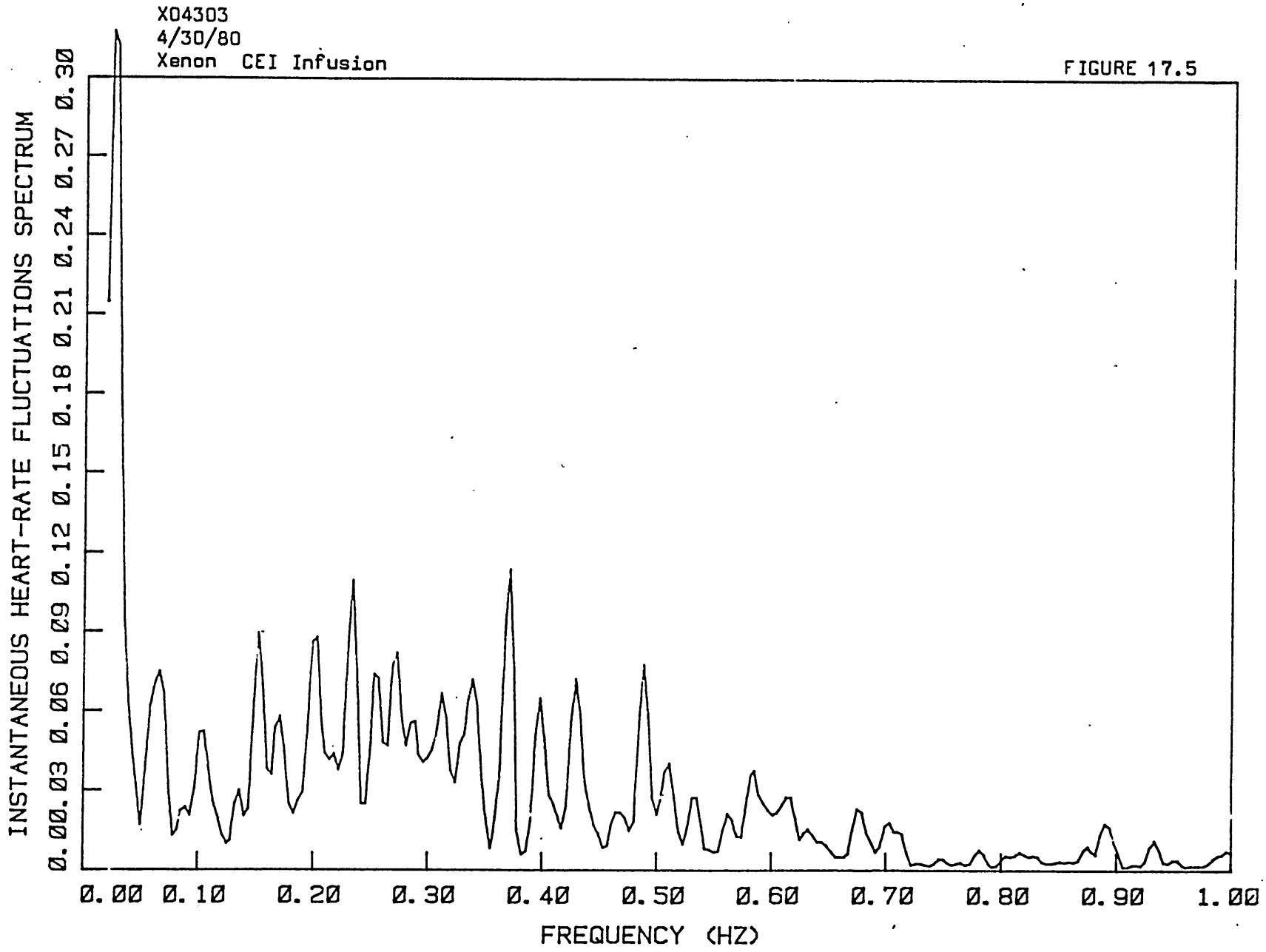
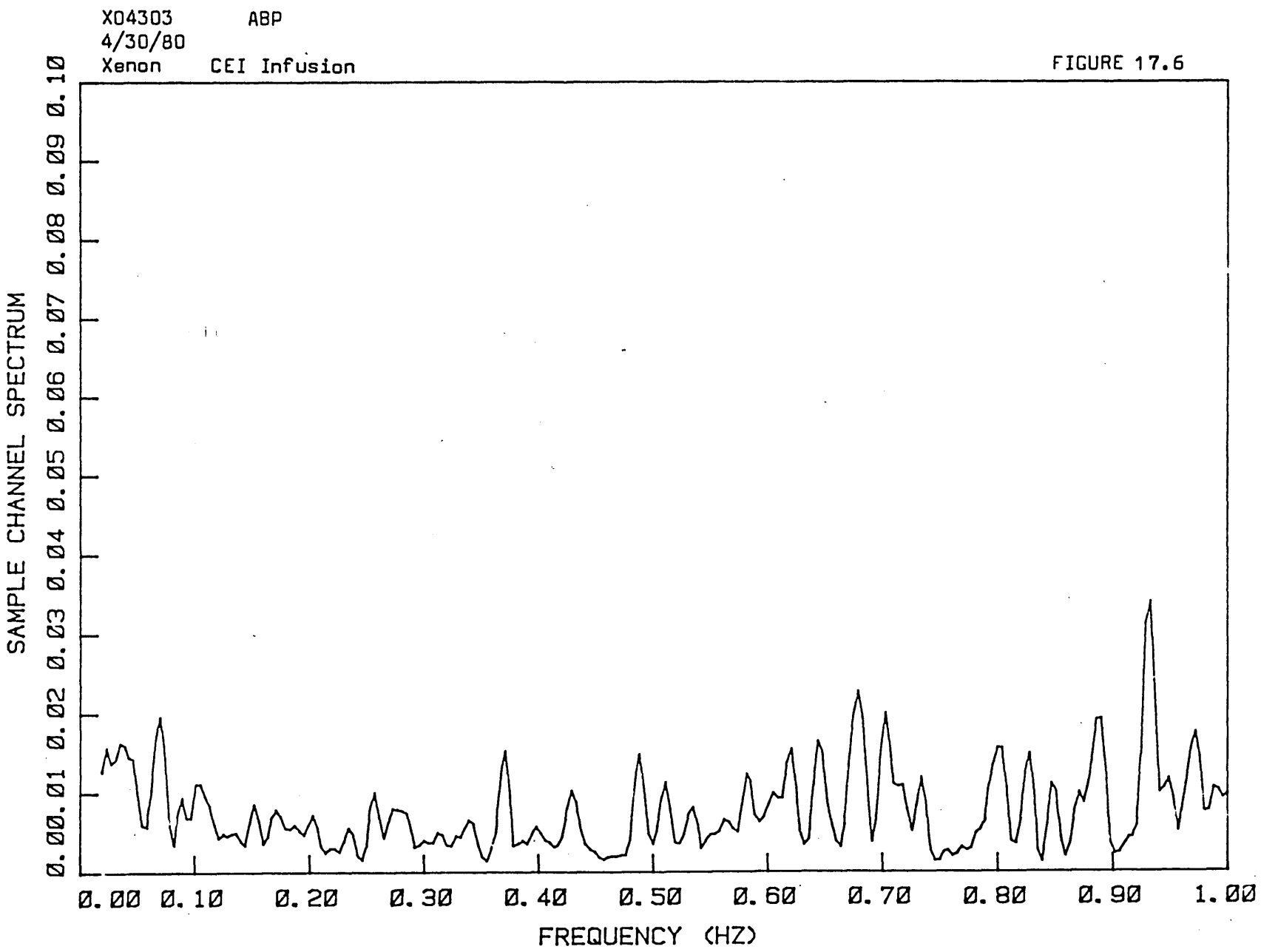

X 10-2
2
1
9
8
7
6
5
4
3
2
1
9
8
7
6
5
4
3
2
1
XENON 4/30/80
RENIN ANGIOTENSIN BLOCKADE
NO BLOCKADE
LOW PEAK AREA
MID PEAK AREA
HEART RATE POWER SPECTRUM
LOW PEAK AREA
MID PEAK AREA
ARTERIAL PRESSURE POWER SPECTRUM

FIGURE 17.2


X04302
4/30/80
Xenon No Drug
FIGURE 17.3
INSTANTANEOUS HEART-RATE FLUCTUATIONS SPECTRUM
0.00 0.03 0.06 0.09 0.12 0.15 0.18 0.21 0.24 0.27 0.30
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)


X04302 ABP
4/30/80
Xenon No Drug
FIGURE 17.4
SAMPLE CHANNEL SPECTRUM
0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.10
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)


X04303
4/30/80
Xenon CEI Infusion
FIGURE 17.5
INSTANTANEOUS HEART-RATE FLUCTUATIONS SPECTRUM
0.00 0.03 0.06 0.09 0.12 0.15 0.18 0.21 0.24 0.27 0.30
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)


X04303 ABP
4/30/80
Xenon CEI Infusion
FIGURE 17.6
SAMPLE CHANNEL SPECTRUM
0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.10
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)

DOG: XENON

DATE OF EXPERIMENT: June 19,1980

BASELINE

DRUG : NONE

INTERVENTION #1

DRUG : .10ug/kg/min Saralasin

INTERVENTION #2

DRUG : .50 ug/kg/min Saralasin

INTERVENTION #3

DRUG : 1.0 ug/kg/min

INTEGRATED AREAS OF SPECTRAL PEAKS

RUN	CHANNEL ANALYZED	LOW FREQ. PEAK	MID FREQ. PEAK	HIGH FREQ. PEAK
Baseline	HR	4.2 E-3	3.0 E-3	1.40 E-2
	A_oP	1.04 E-4	2.62 E-3	3.65 E-3
	Resp	1.42 E-3	6.98 E-4	1.59 E-3
INT. #1	HR	1.5 E-3	0.87 E-3	0.665 E-2
	A_oP	1.47 E-4	1.09 E-3	4.50 E-3
	Resp	3.22 E-3	15.6 E-4	8.01 E-3
INT. #2	HR	1.69 E-3	1.0 E-3	0.35 E-2
	A_oP	1.82 E-4	5.09 E-4	4.33 E-3
	Resp	0.95 E-3	6.07 E-4	1.93 E-3
INT. #3	HR	9.83 E-3	3.1 E-3	0.51 E-2
	A_oP	4.69 E-4	7.07 E-4	1.57 E-3
	Resp	1.77 E-3	9.48 E-4	0.28 E-3

FIGURE 18.01

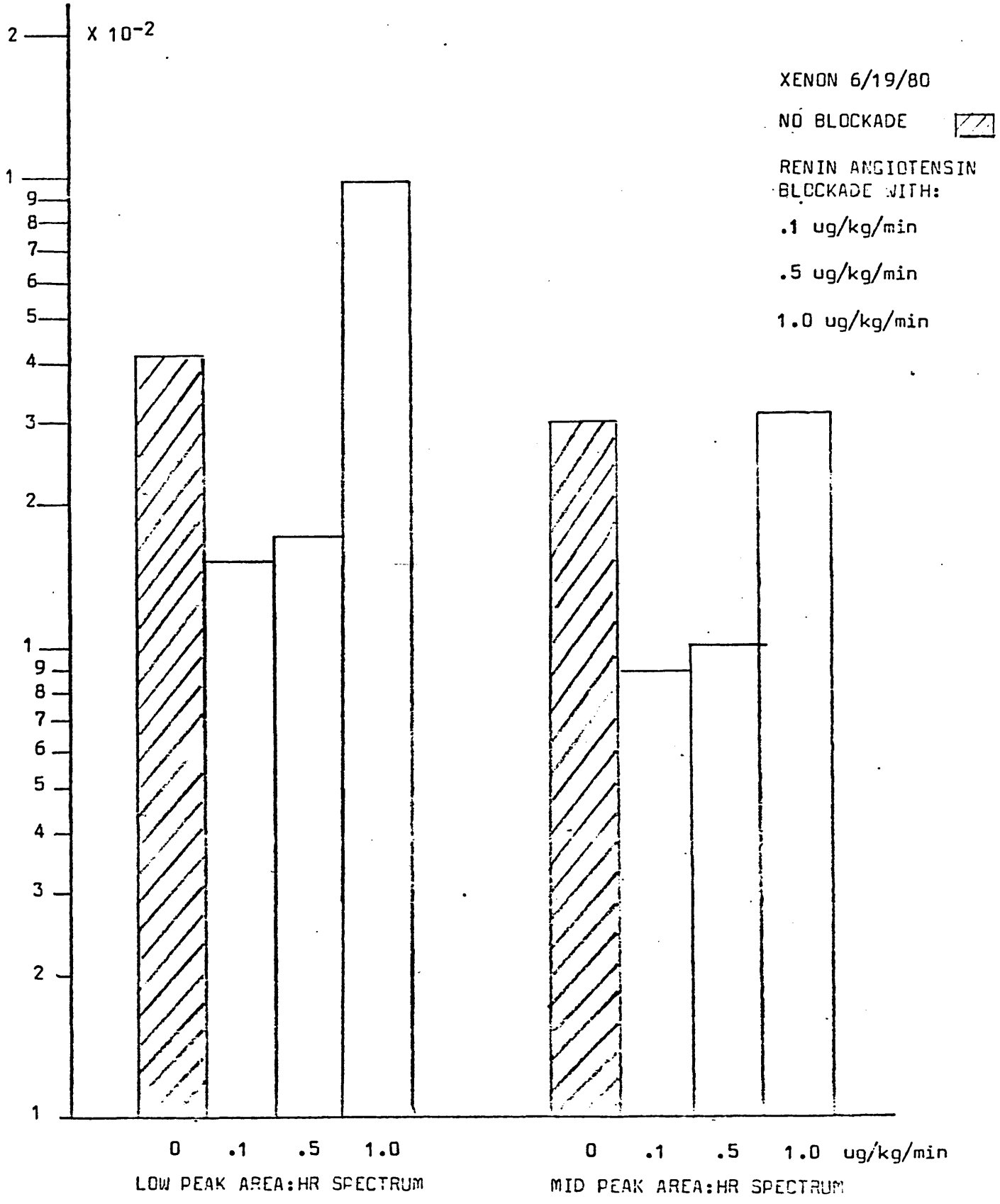
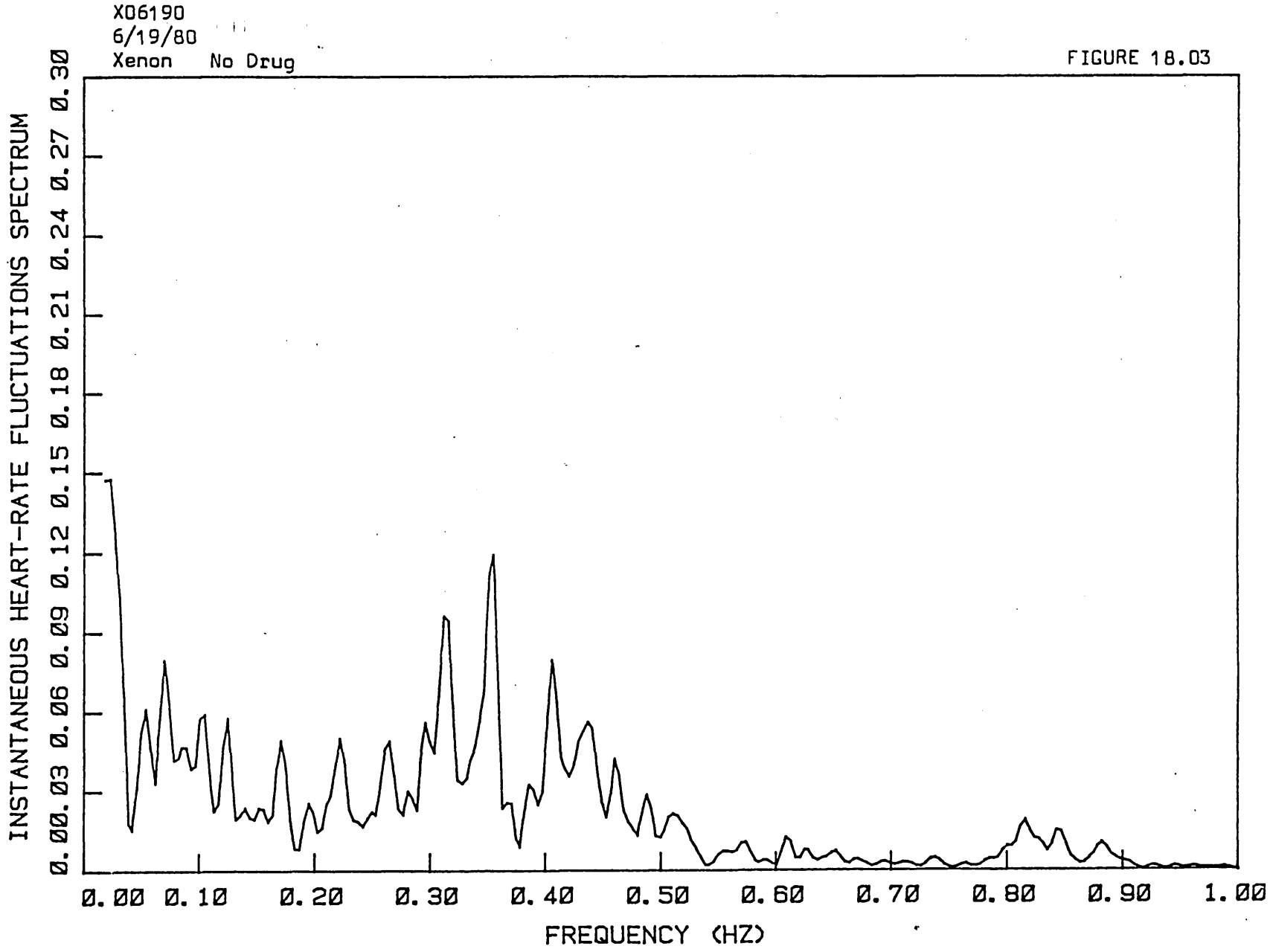
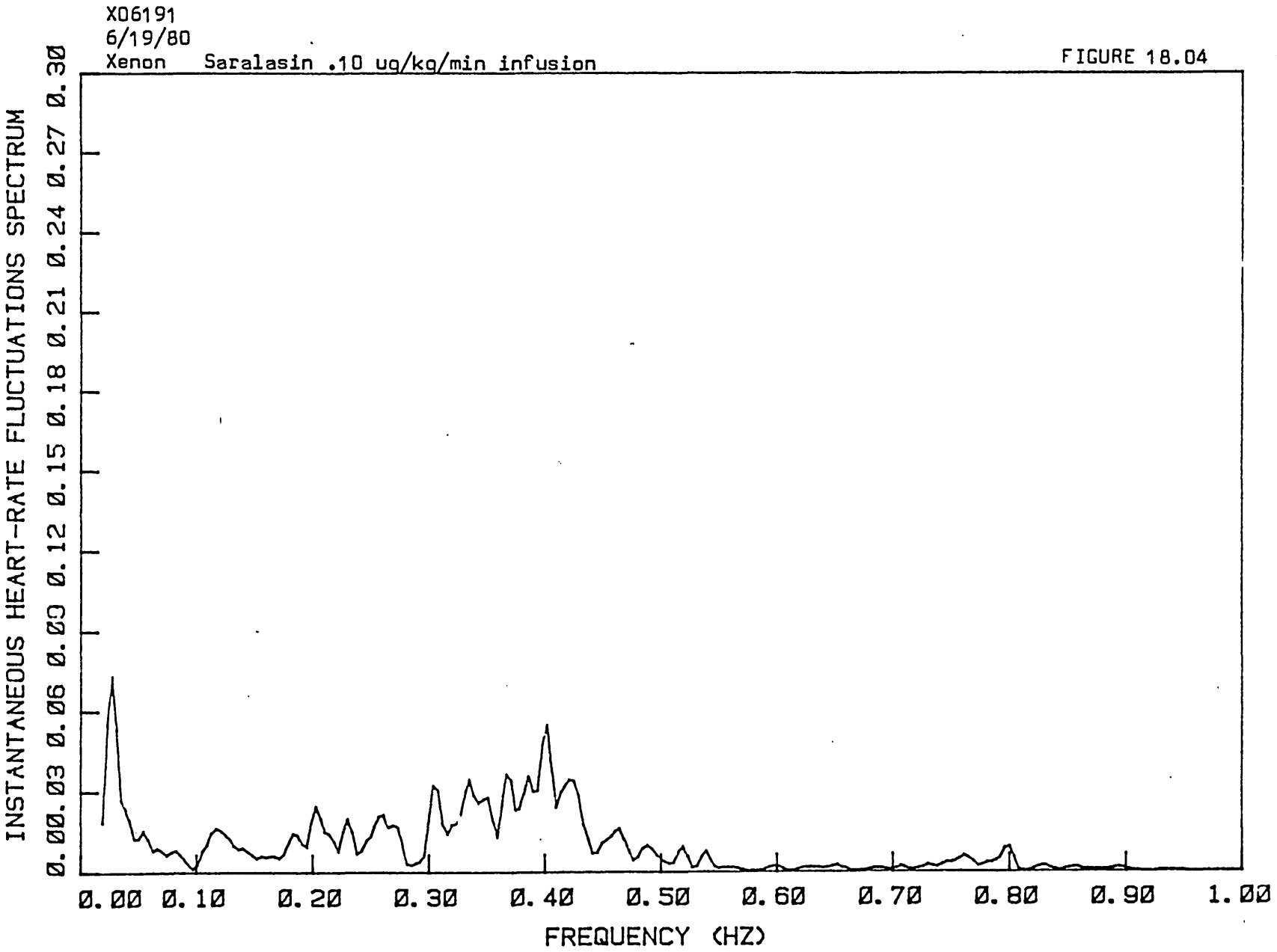
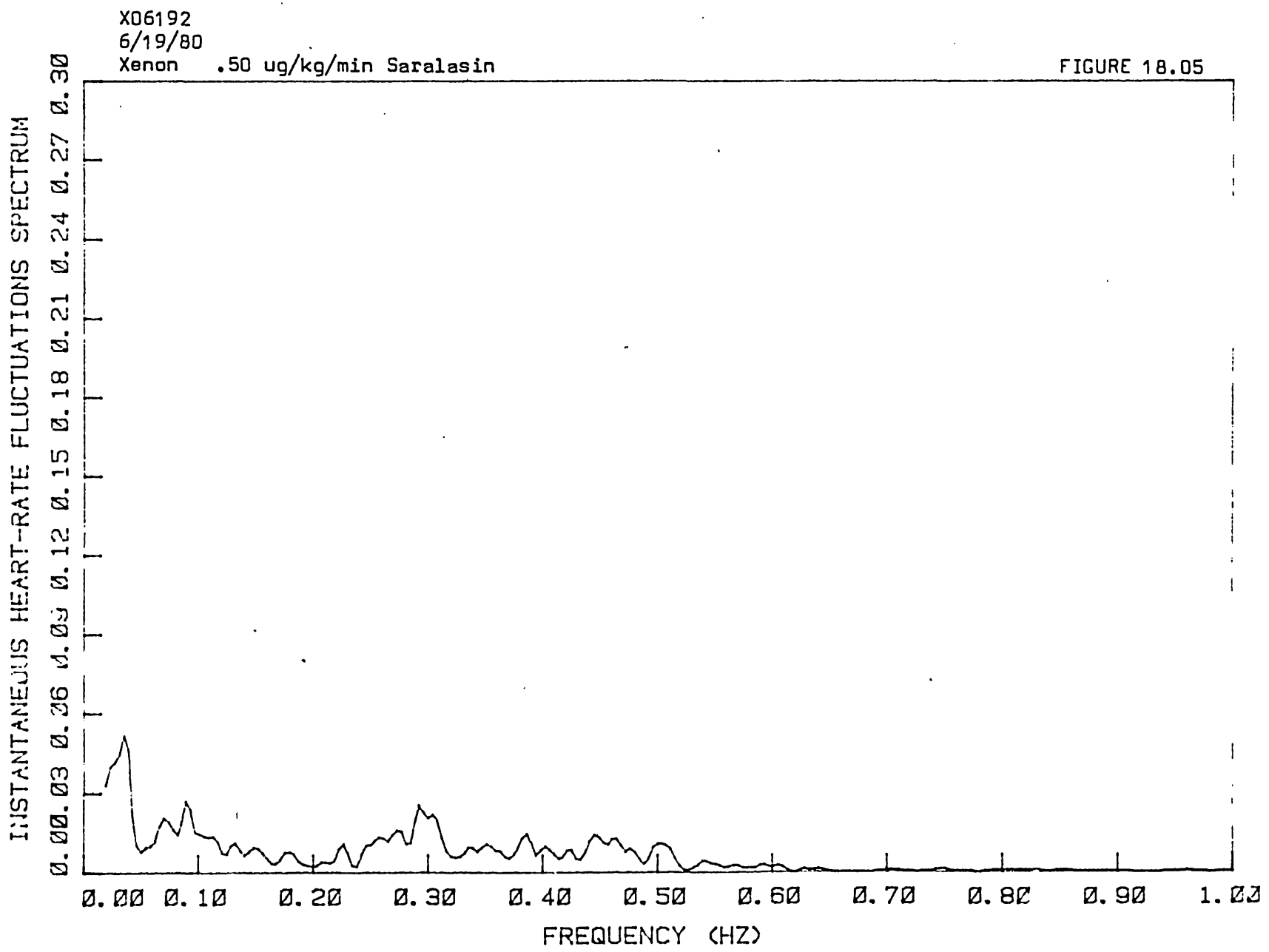
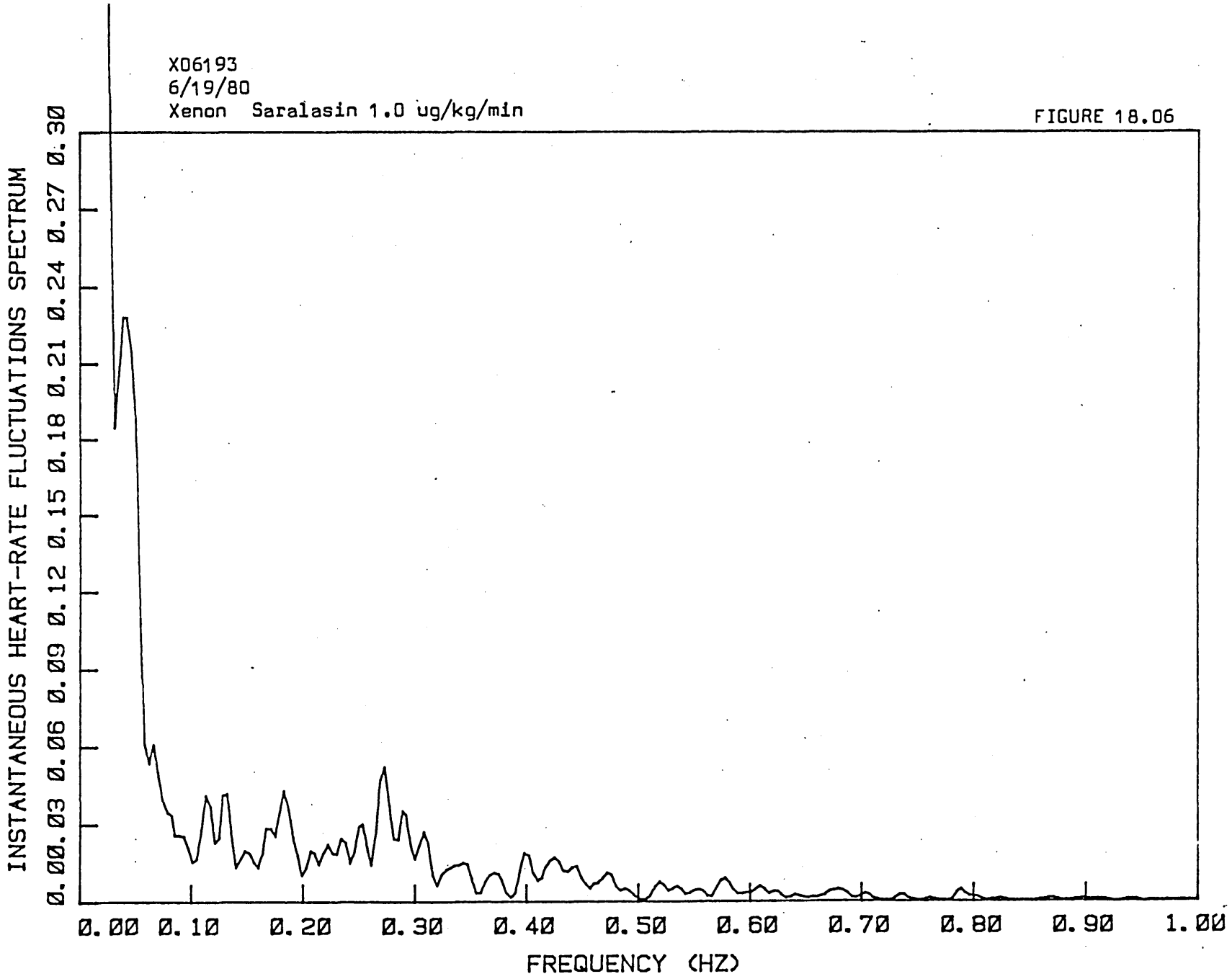

X 10-2
2
1
9
8
7
6
5
4
3
2
1
9
8
7
6
5
4
3
2
1
XENON 6/19/80
NO BLOCKADE
RENIN ANGIOTENSIN BLOCKADE WITH:
.1 ug/kg/min
.5 ug/kg/min
1.0 ug/kg/min
0 .1 .5 1.0
0 .1 .5 1.0 ug/kg/min
LOW PEAK AREA:HR SPECTRUM
MID PEAK AREA:HR SPECTRUM

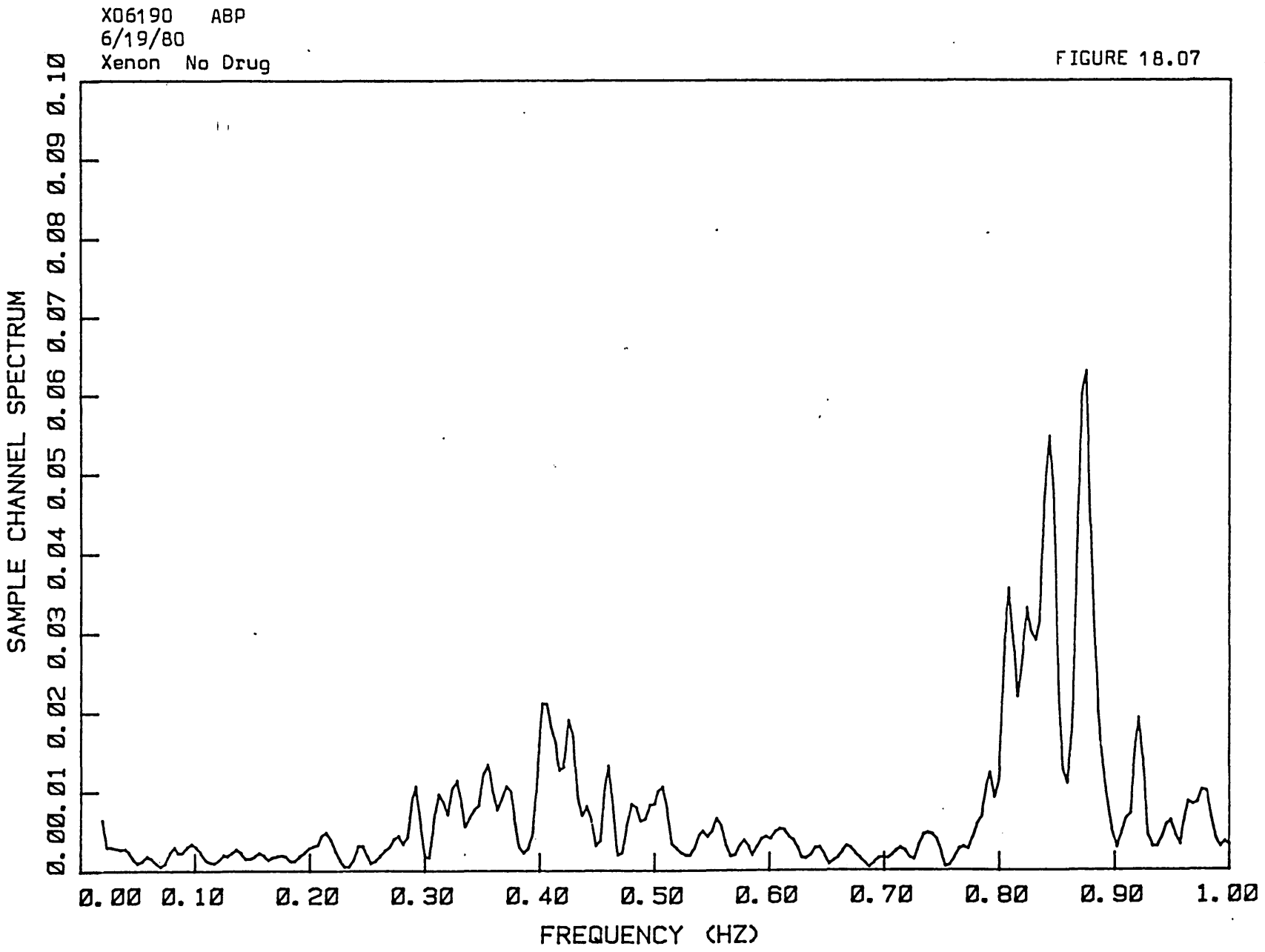
FIGURE 18.02

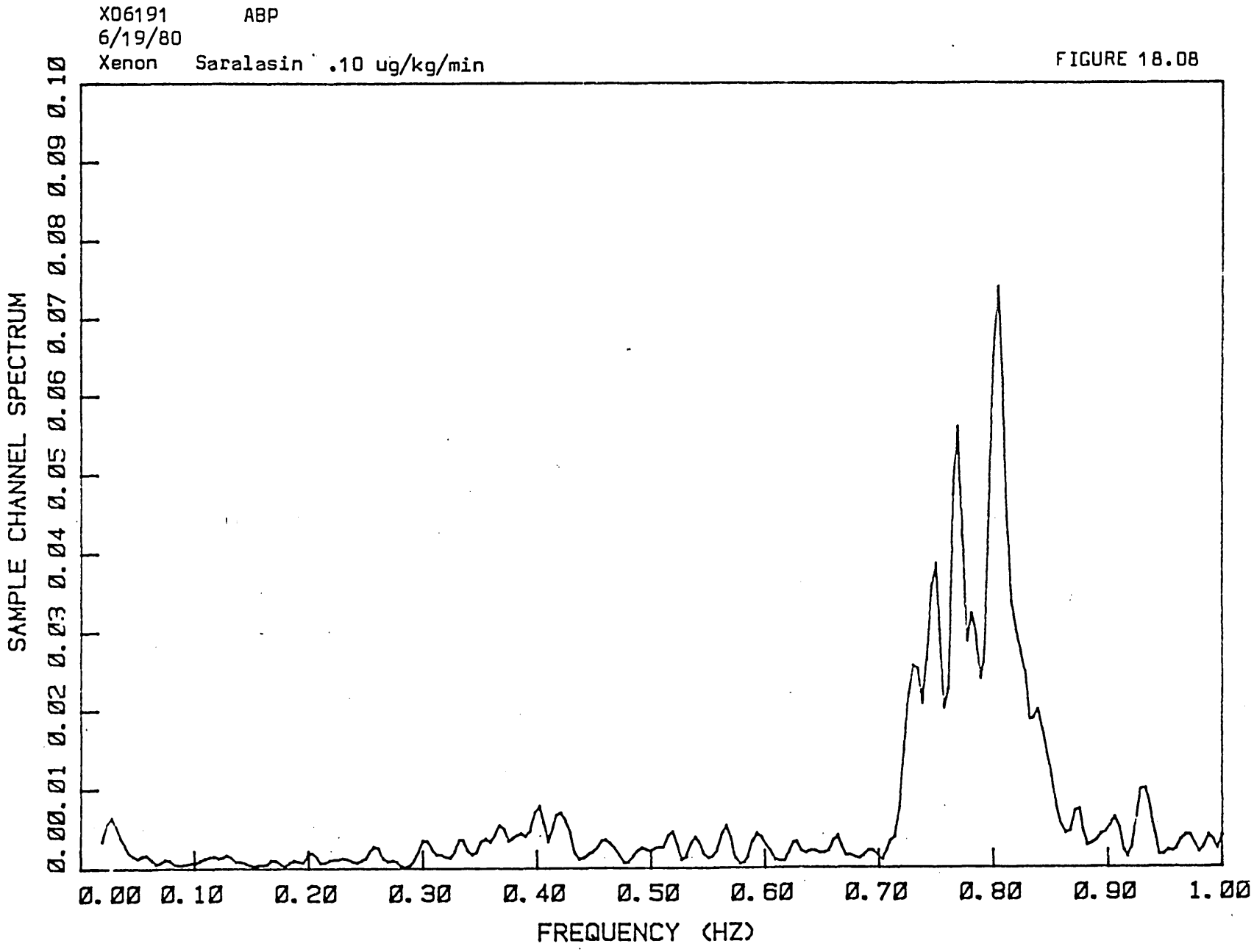

X06190
6/19/80
Xenon No Drug
FIGURE 18.03
INSTANTANEOUS HEART-RATE FLUCTUATIONS SPECTRUM
0.00 0.03 0.06 0.09 0.12 0.15 0.18 0.21 0.24 0.27 0.30
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)


X06191
6/19/80
Xenon Saralasin .10 ug/kg/min infusion
FIGURE 18.04
INSTANTANEOUS HEART-RATE FLUCTUATIONS SPECTRUM
0.00 0.03 0.06 0.09 0.12 0.15 0.18 0.21 0.24 0.27 0.30
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)


X06192
6/19/80
Xenon .50 ug/kg/min Saralasin
FIGURE 18.05
INSTANTANEOUS HEART-RATE FLUCTUATIONS SPECTRUM
0.00 0.03 0.06 0.09 0.12 0.15 0.18 0.21 0.24 0.27 0.30
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)

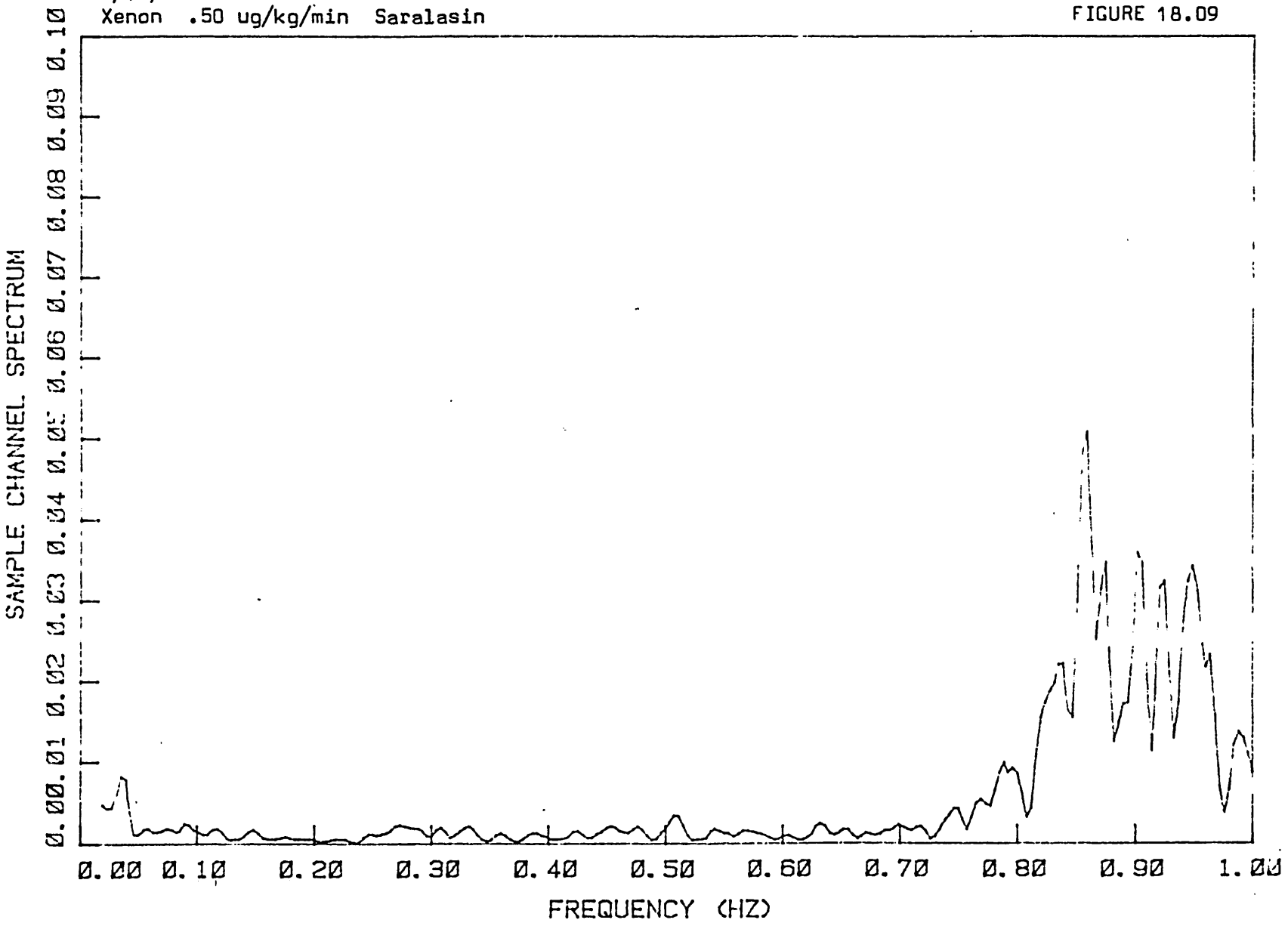

X06193
6/19/80
Xenon Saralasin 1.0 ug/kg/min
FIGURE 18.06
INSTANTANEOUS HEART-RATE FLUCTUATIONS SPECTRUM
0.00 0.03 0.06 0.09 0.12 0.15 0.18 0.21 0.24 0.27 0.30
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)

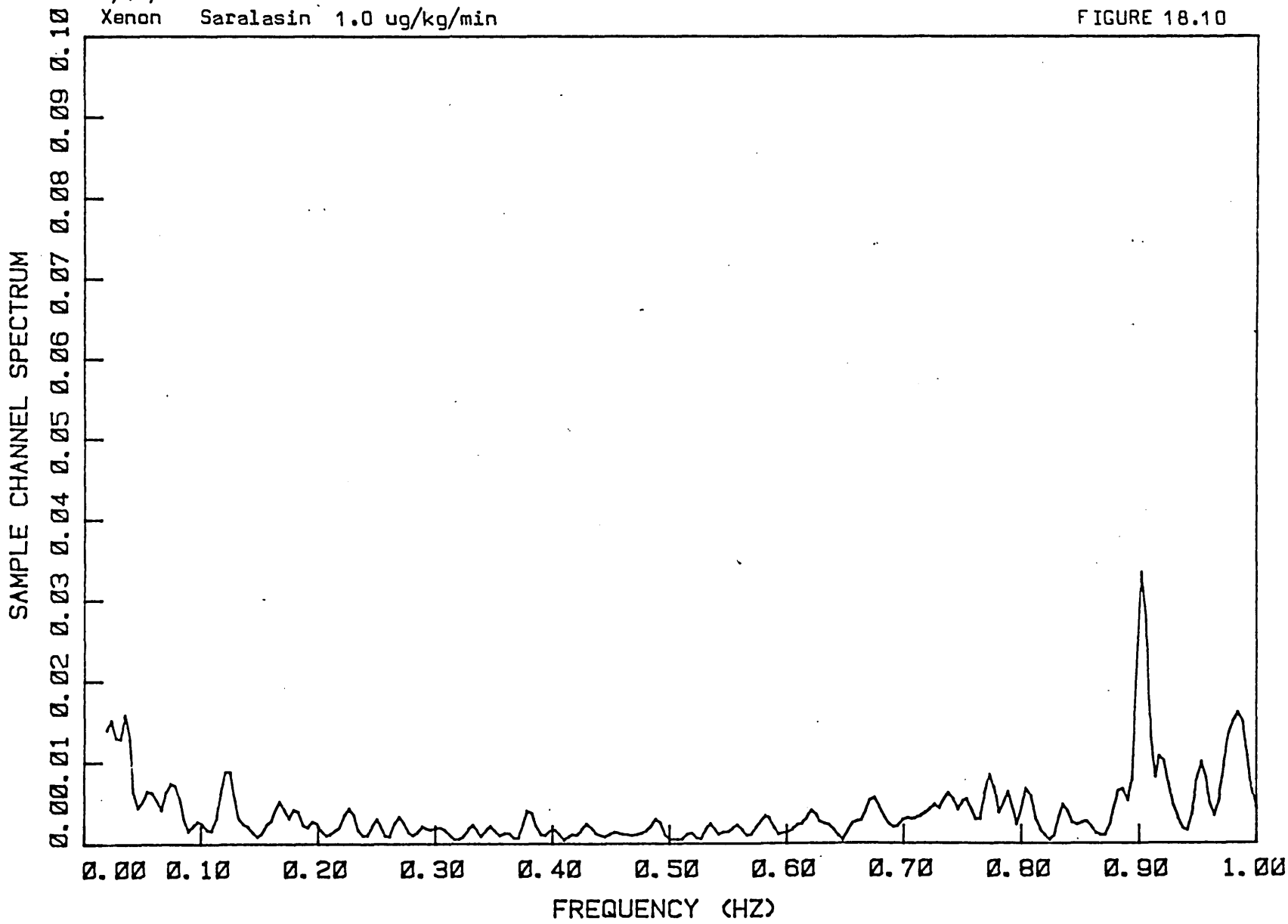

X06190 ABP
6/19/80
Xenon No Drug
FIGURE 18.07
SAMPLE CHANNEL SPECTRUM
0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.10
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)


X06191 ABP
6/19/80
Xenon Saralasin .10 ug/kg/min
FIGURE 18.08
SAMPLE CHANNEL SPECTRUM
0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.10
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)

X06192 ABP
6/19/80
Xenon .50 ug/kg/min Saralasin

FIGURE 18.09




X06193 ABP
6/19/80
Xenon Saralasin 1.0 ug/kg/min
FIGURE 18.10
SAMPLE CHANNEL SPECTRUM
0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.10
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)

DOG: XENON

DATE OF EXPERIMENT: June 21,1980

BASELINE

DRUG : NONE

INTERVENTION #1

DRUG : 1.0 ug/kg/min Saralasin

INTERVENTION #2

DRUG : 5.0 ug/kg/min Saralasin

INTERVENTION #3

DRUG : 10.0 ug/kg/min Saralasin

INTEGRATED AREAS OF SPECTRAL PEAKS

RUN	CHANNEL ANALYZED	LOW FREQ. PEAK	MID FREQ. PEAK	HIGH FREQ. PEAK
Baseline	HR	.574 E-3	.581 E-3	.51 E-3
	A_oP	2.83 E-4	1.30 E-4	1.70 E-4
	Resp	1.06 E-3	.655 E-3	.515 E-3
INT. #1	HR	.975 E-3	.868 E-3	1.46 E-3
	A_oP	.846 E-4	.506 E-4	.80 E-4
	Resp	3.00 E-3	1.29 E-3	1.45 E-2
INT. #2	HR	.524 E-3	1.66 E-3	8.67 E-3
	A_oP	2.10 E-4	1.97 E-4	4.02 E-3
	Resp	2.79 E-3	2.09 E-3	1.97 E-2
INT. #3	HR	2.35 E-3	1.87 E-3	2.32 E-2
	A_oP	7.44 E-4	3.46 E-4	10.16 E-3
	Resp	2.76 E-3	1.18 E-3	1.25 E-2

FIGURE 19.01

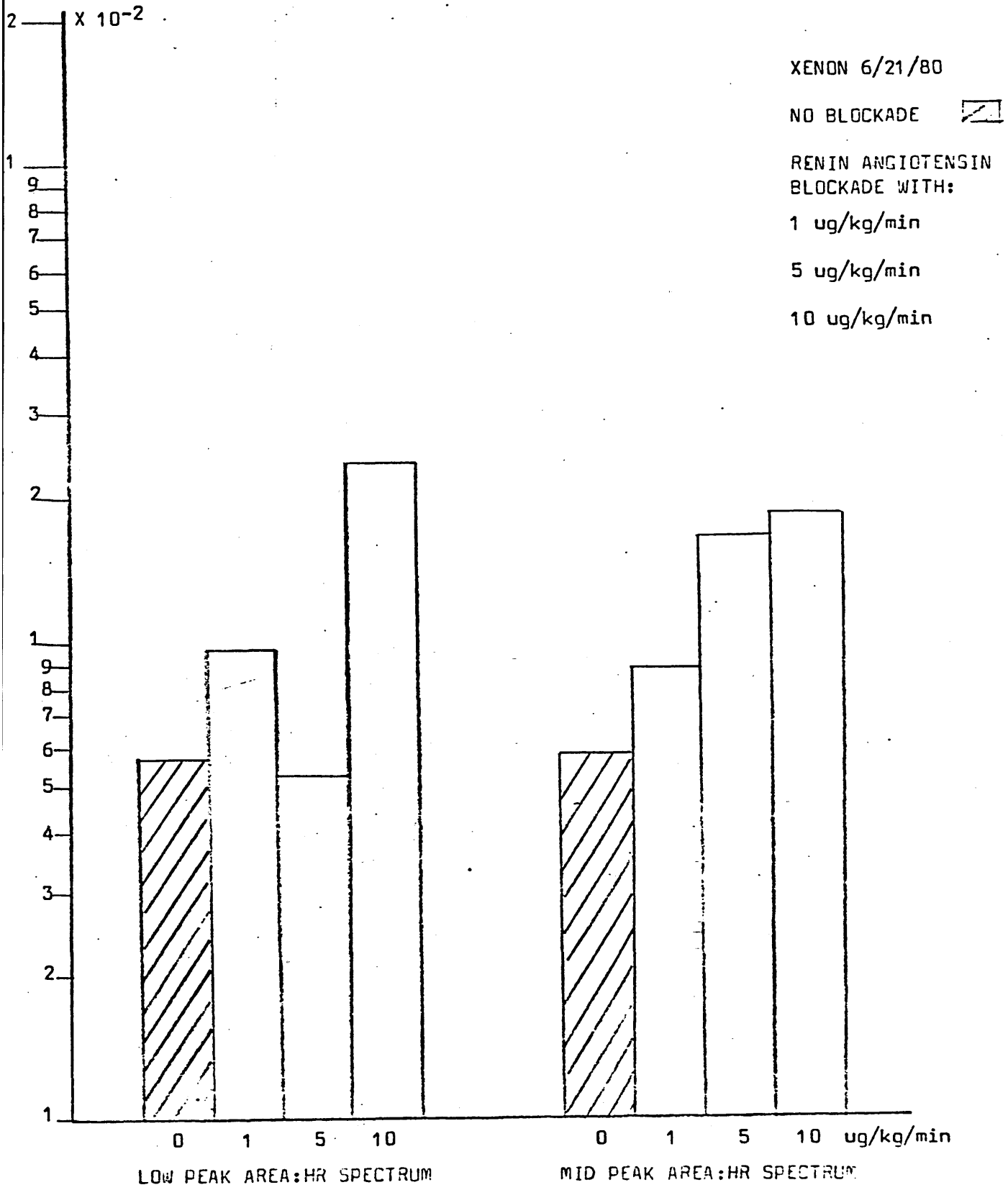
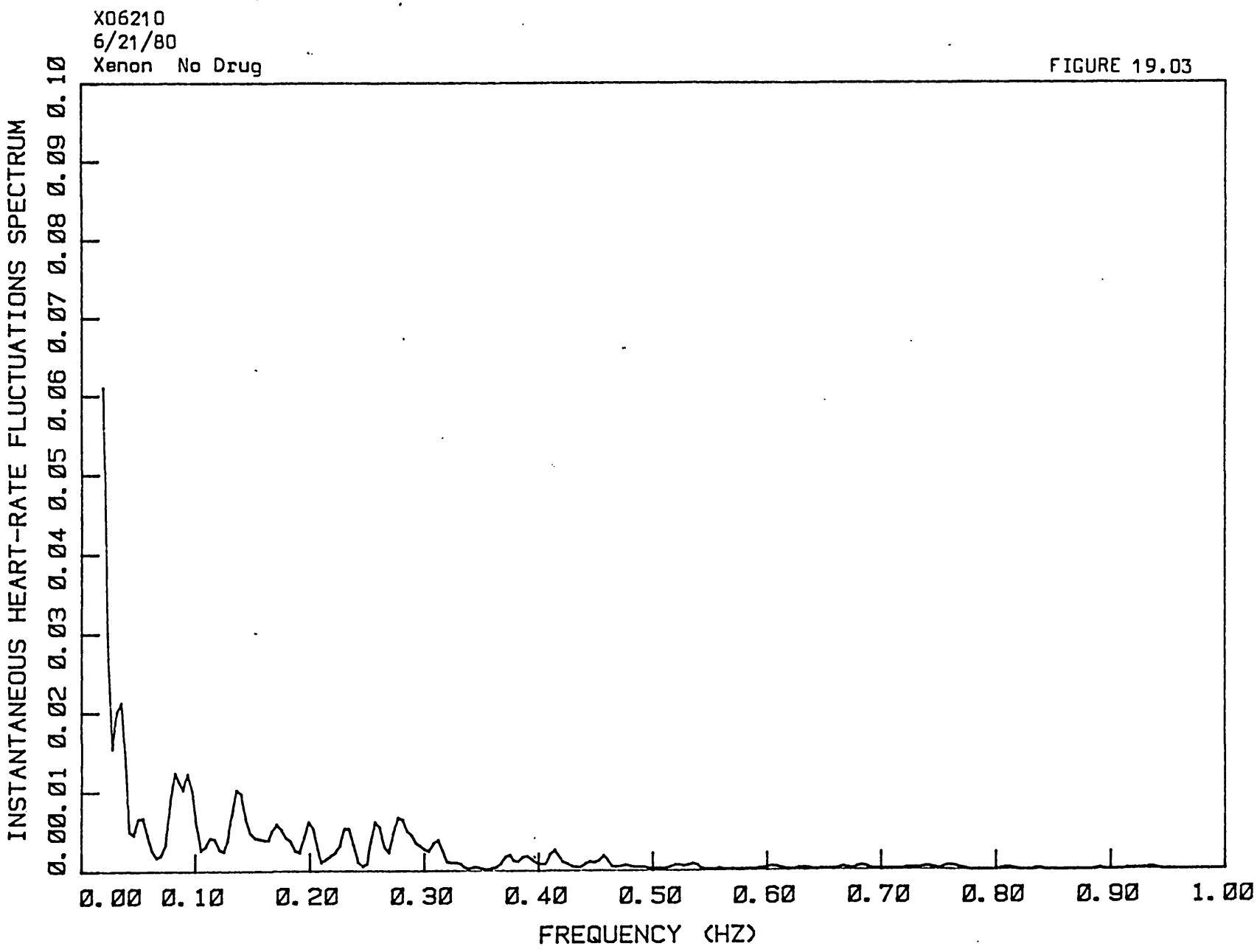
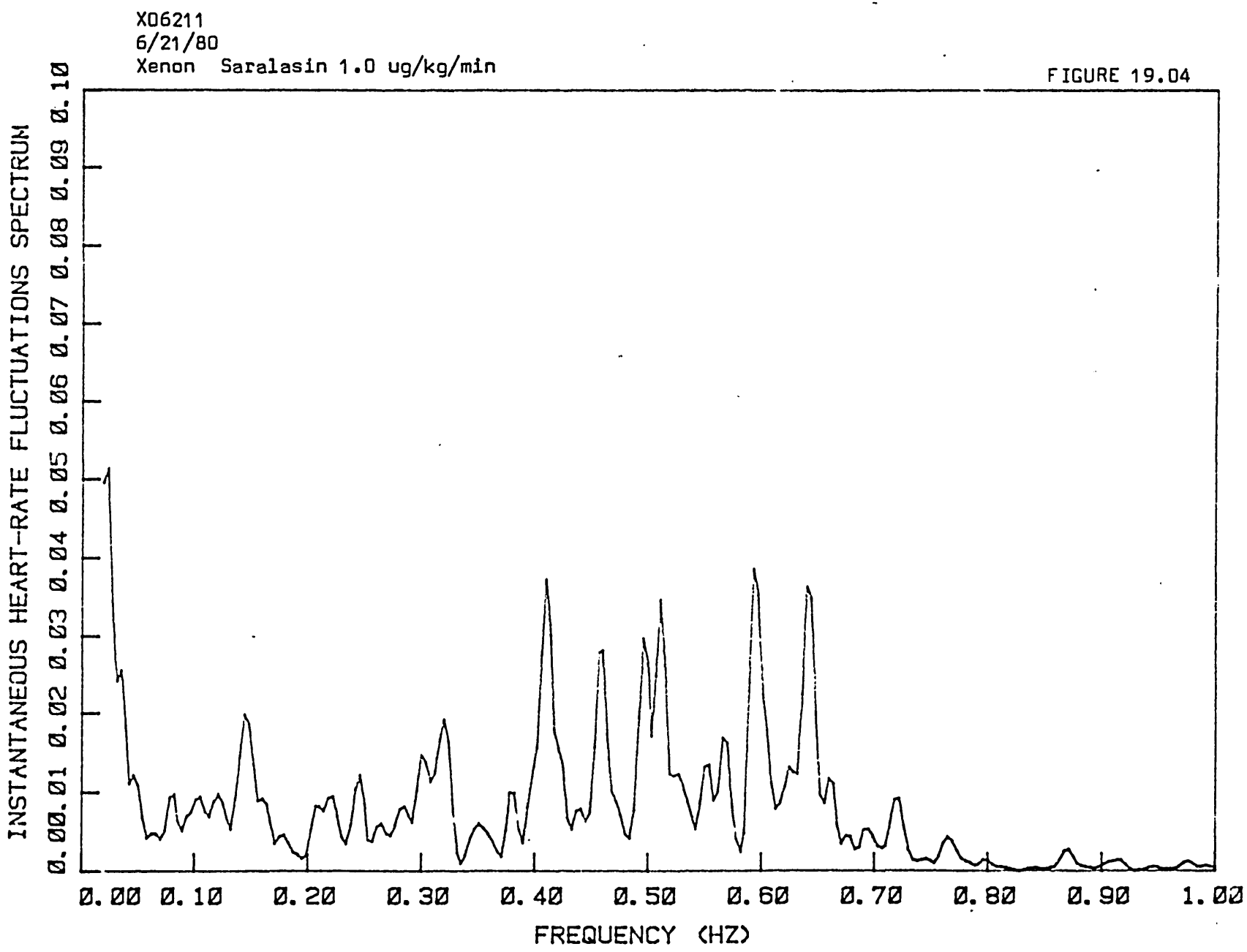
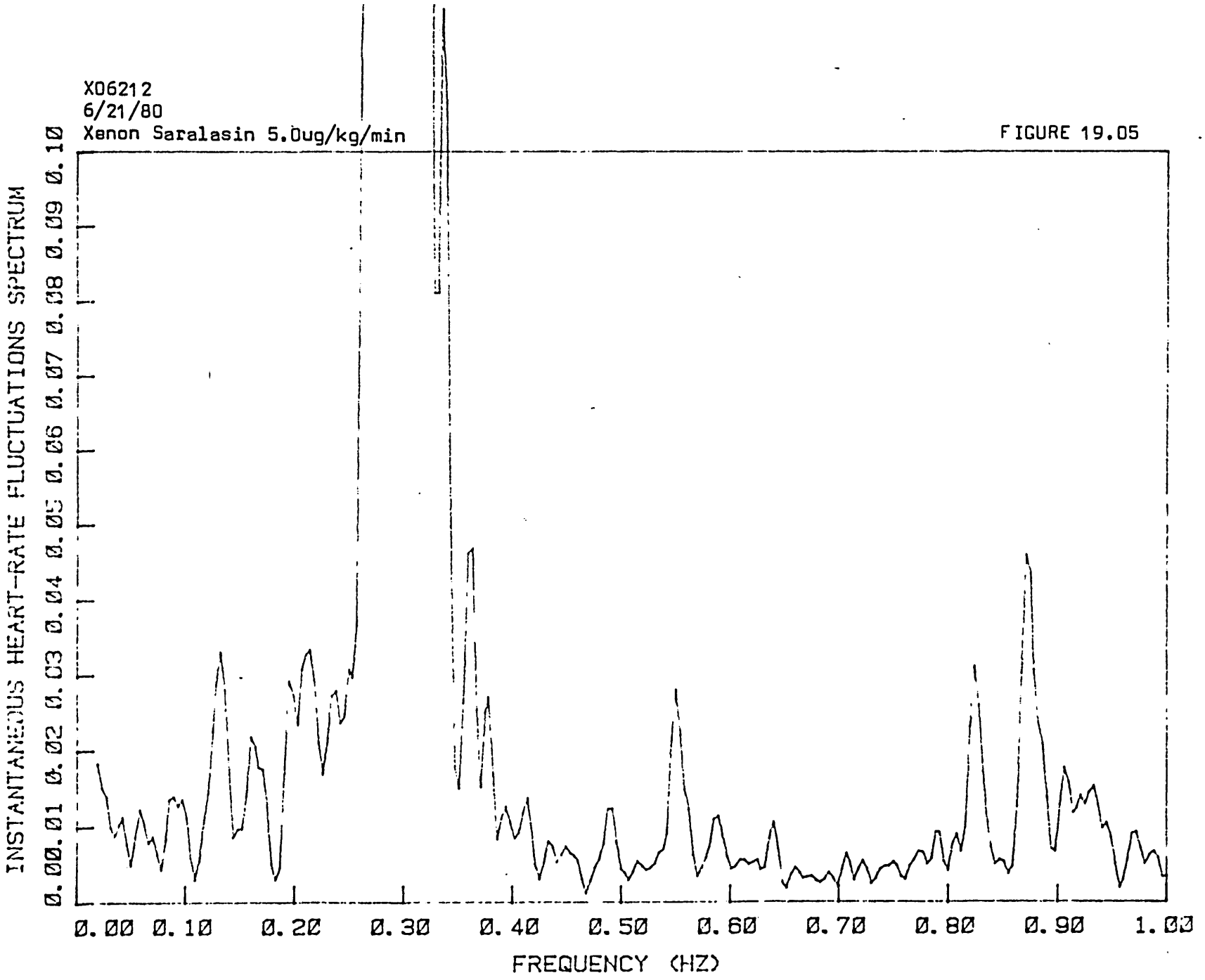
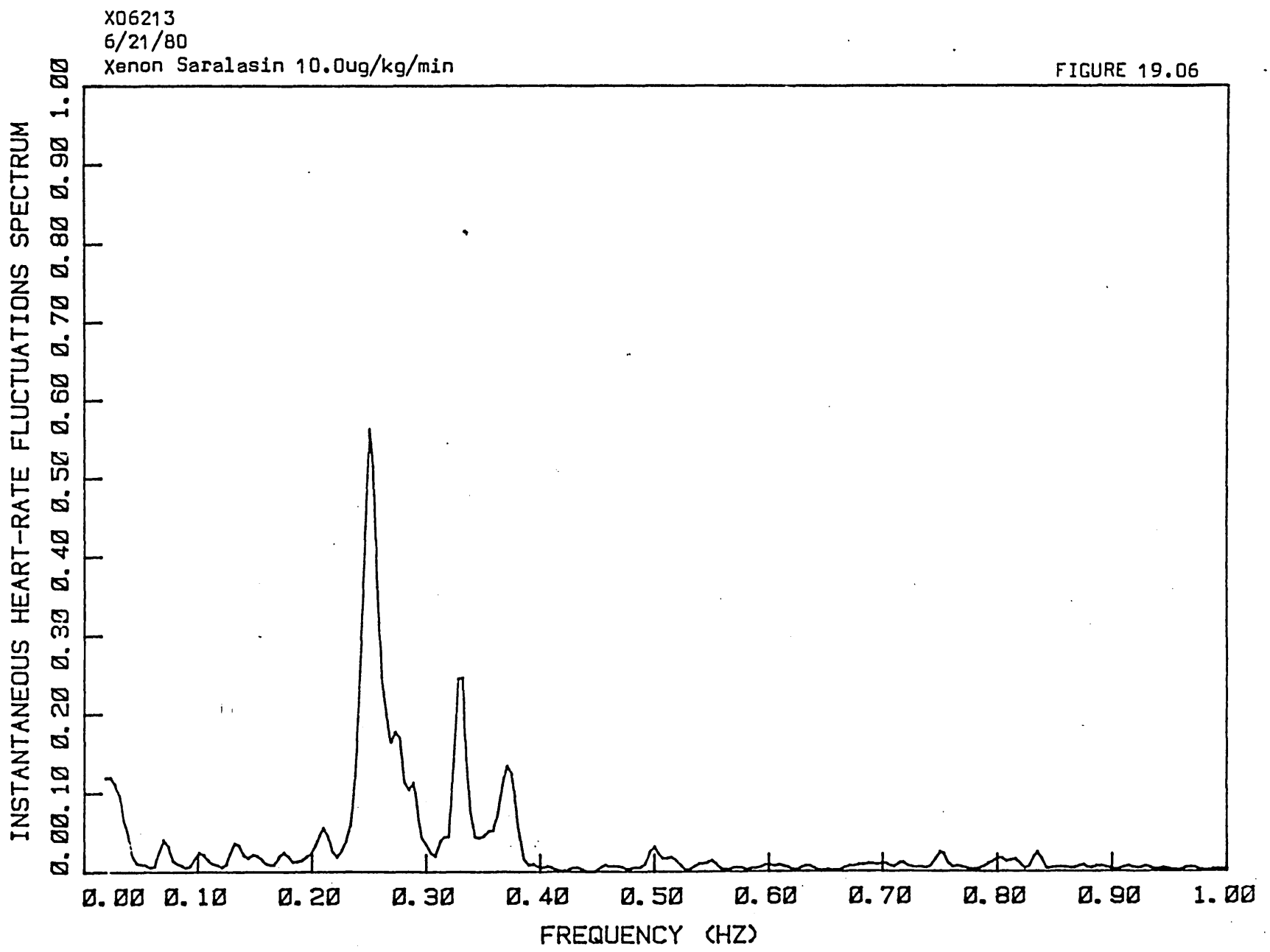

X 10-2
2
1
9
8
7
6
5
4
3
2
1
9
8
7
6
5
4
3
2
1
XENON 6/21/80
NO BLOCKADE
RENIN ANGIOTENSIN BLOCKADE WITH:
1 ug/kg/min
5 ug/kg/min
10 ug/kg/min
0 1 5 10
0 1 5 10 ug/kg/min
LOW PEAK AREA:HR SPECTRUM
MID PEAK AREA:HR SPECTRUM

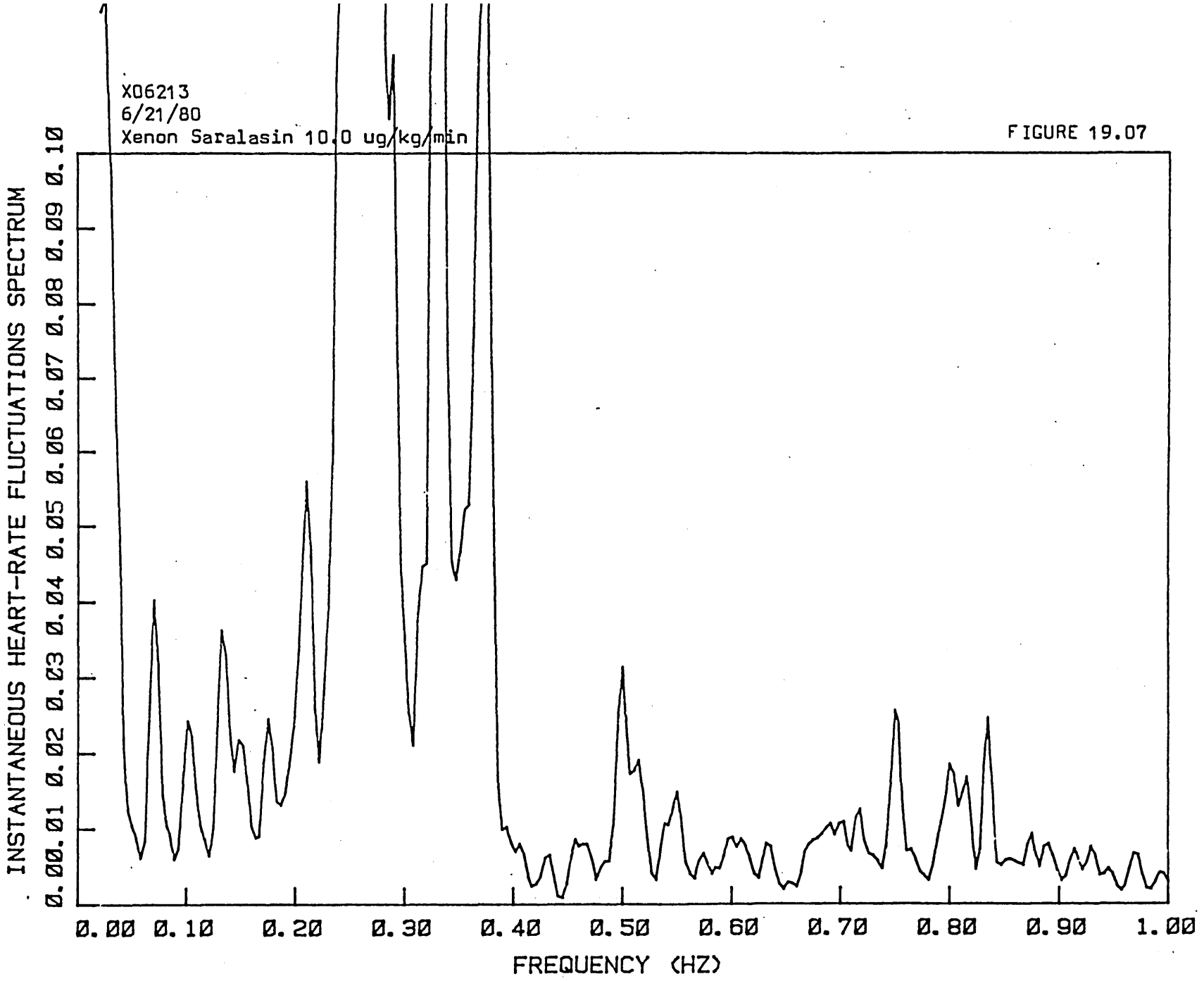
FIGURE 19.62

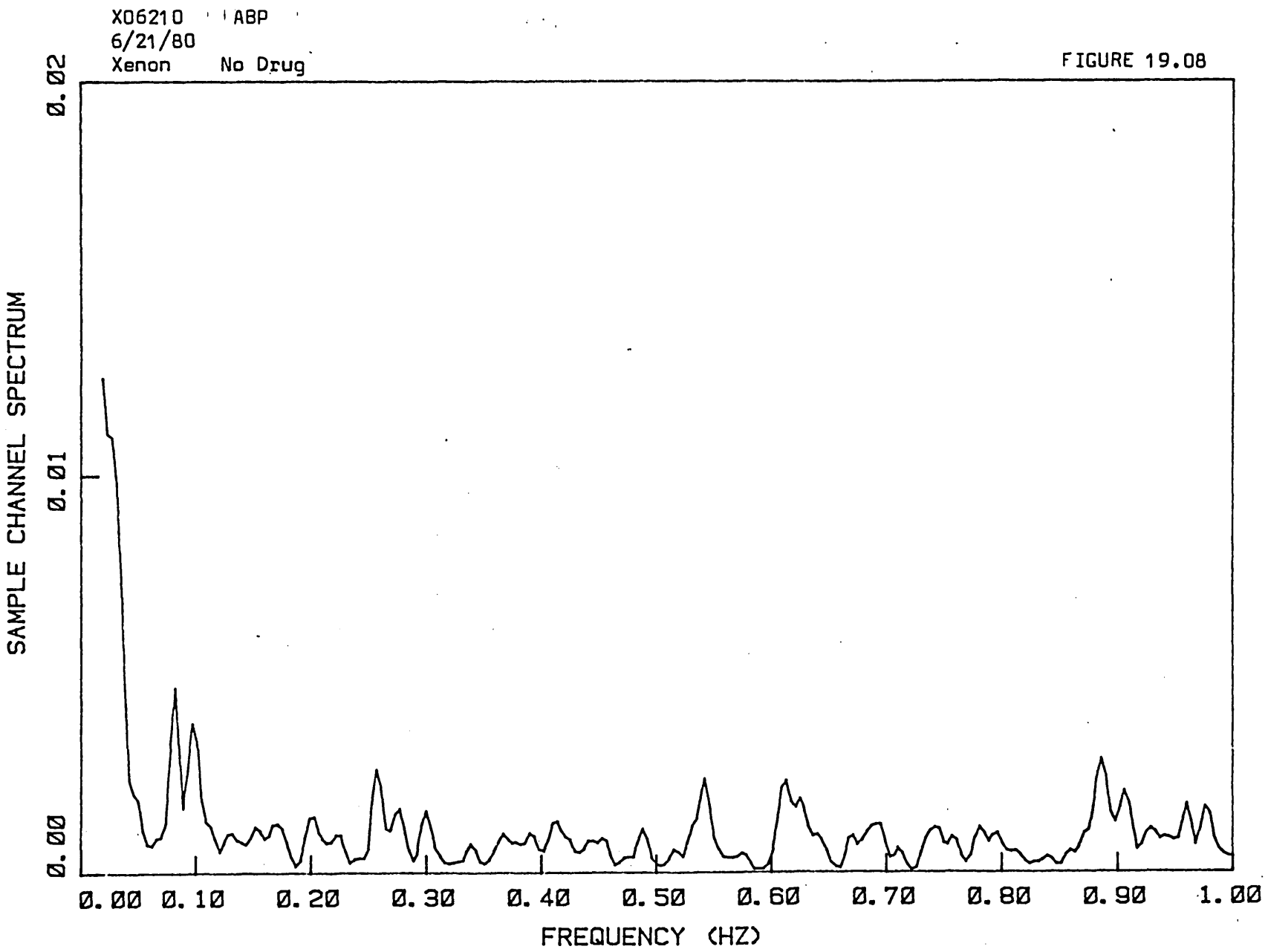

X06210
6/21/80
Xenon No Drug
FIGURE 19.03
INSTANTANEOUS HEART-RATE FLUCTUATIONS SPECTRUM
0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.10
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)

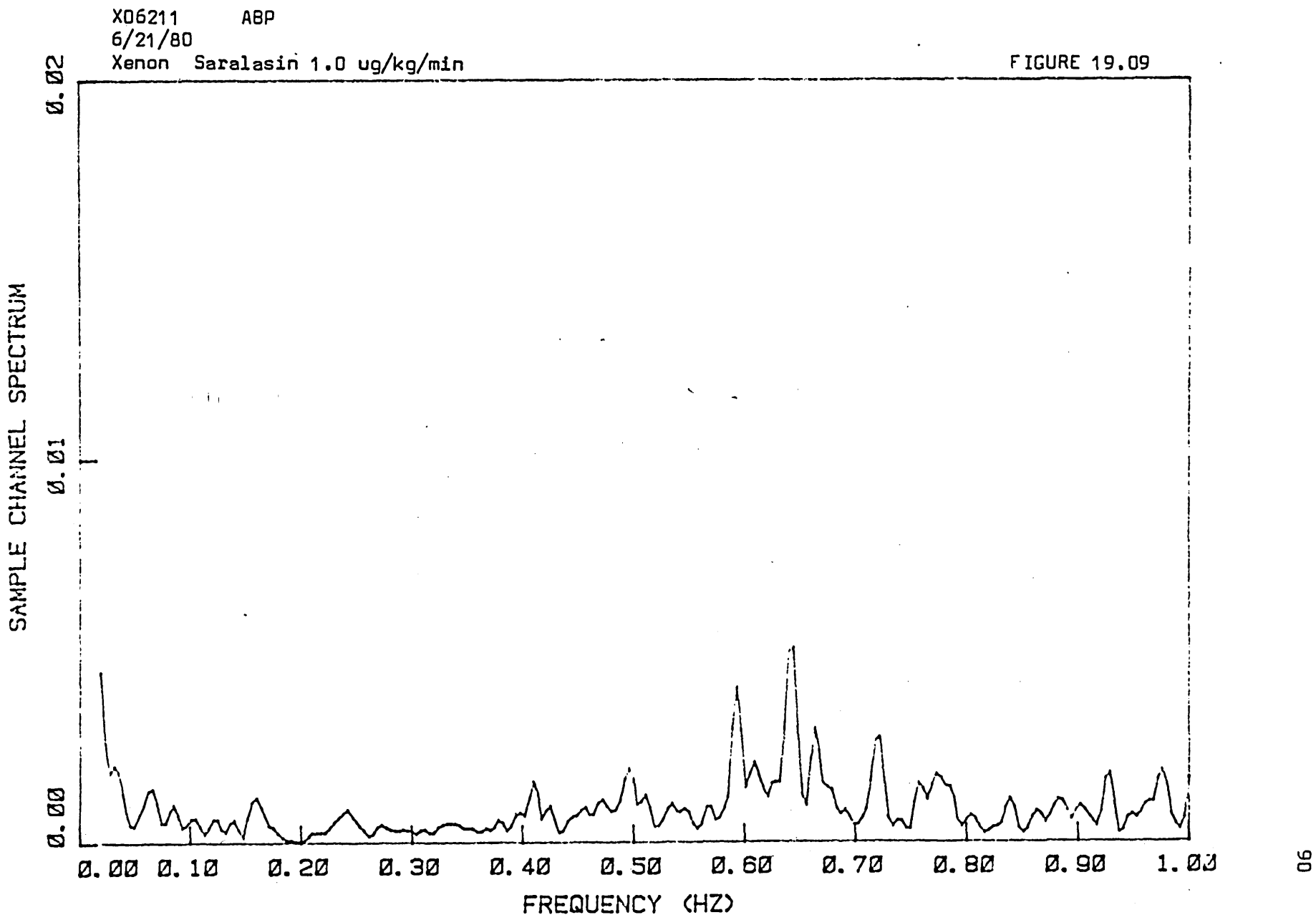

X06211
6/21/80
Xenon Saralasin 1.0 ug/kg/min
FIGURE 19.04
INSTANTANEOUS HEART-RATE FLUCTUATIONS SPECTRUM
0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.10
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)

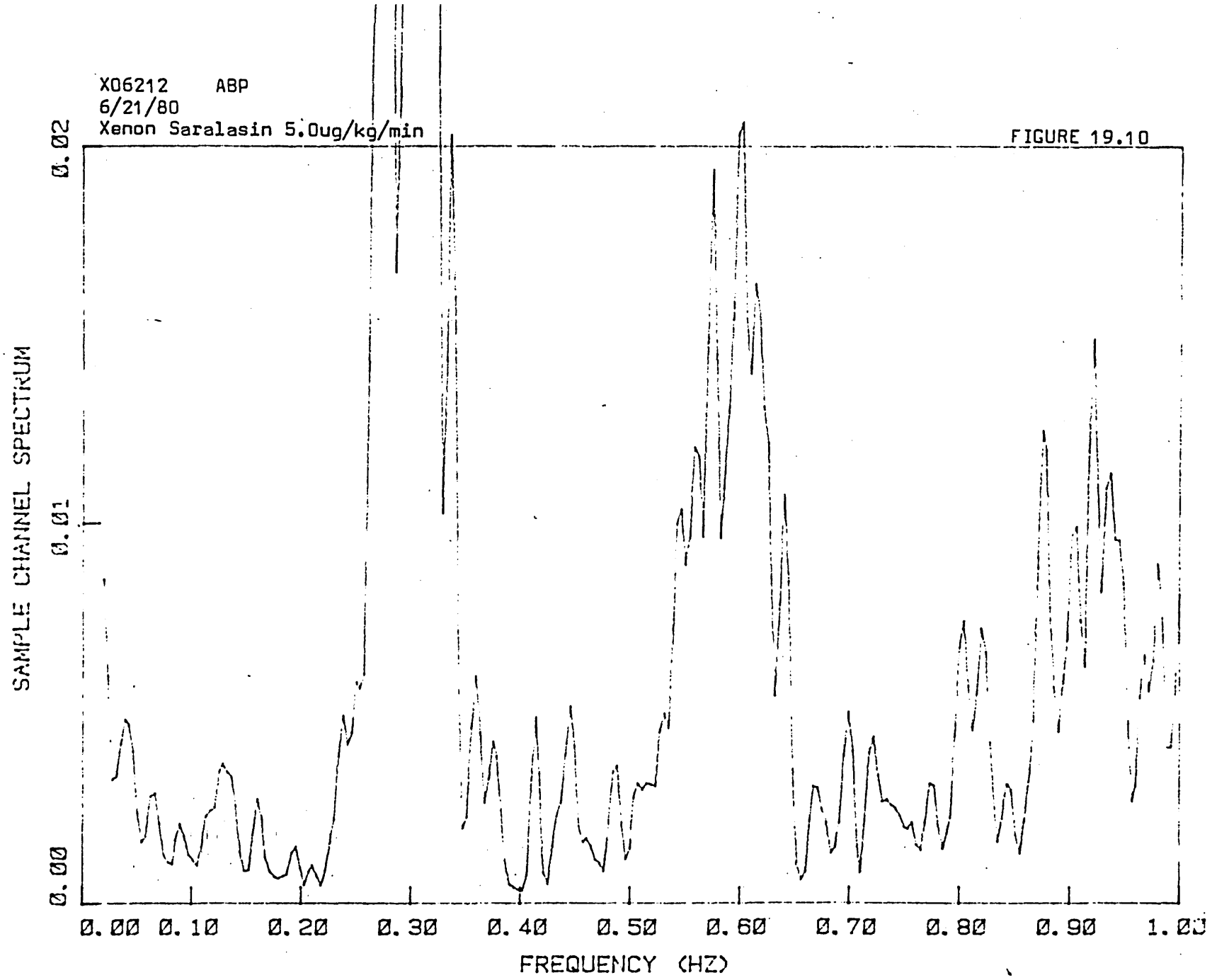

X06212
6/21/80
Xenon Saralasin 5.0ug/kg/min
FIGURE 19.05
INSTANTANEOUS HEART-RATE FLUCTUATIONS SPECTRUM
0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.10
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)

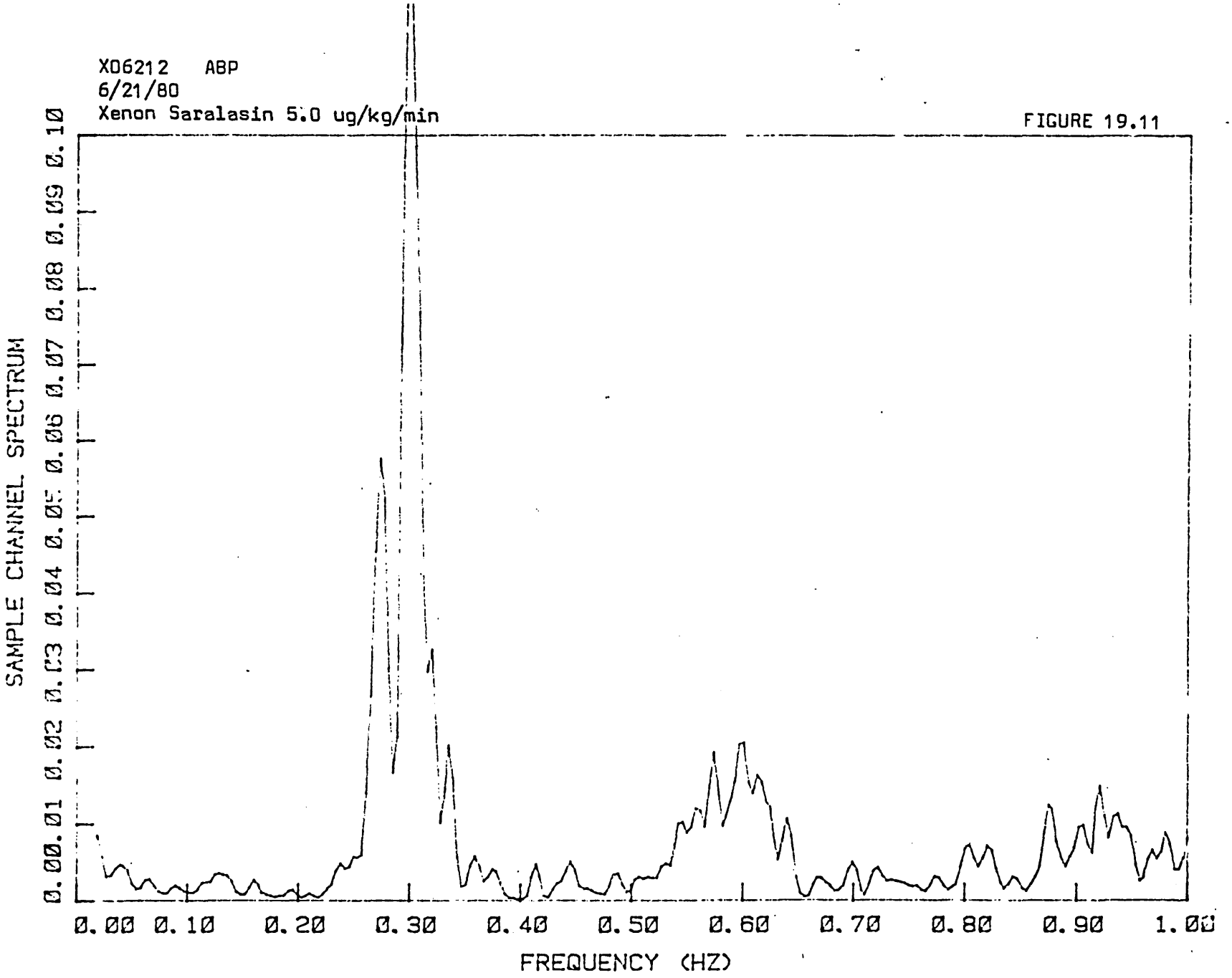

X06213
6/21/80
Xenon Saralasin 10.0ug/kg/min
FIGURE 19.06
INSTANTANEOUS HEART-RATE FLUCTUATIONS SPECTRUM
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)

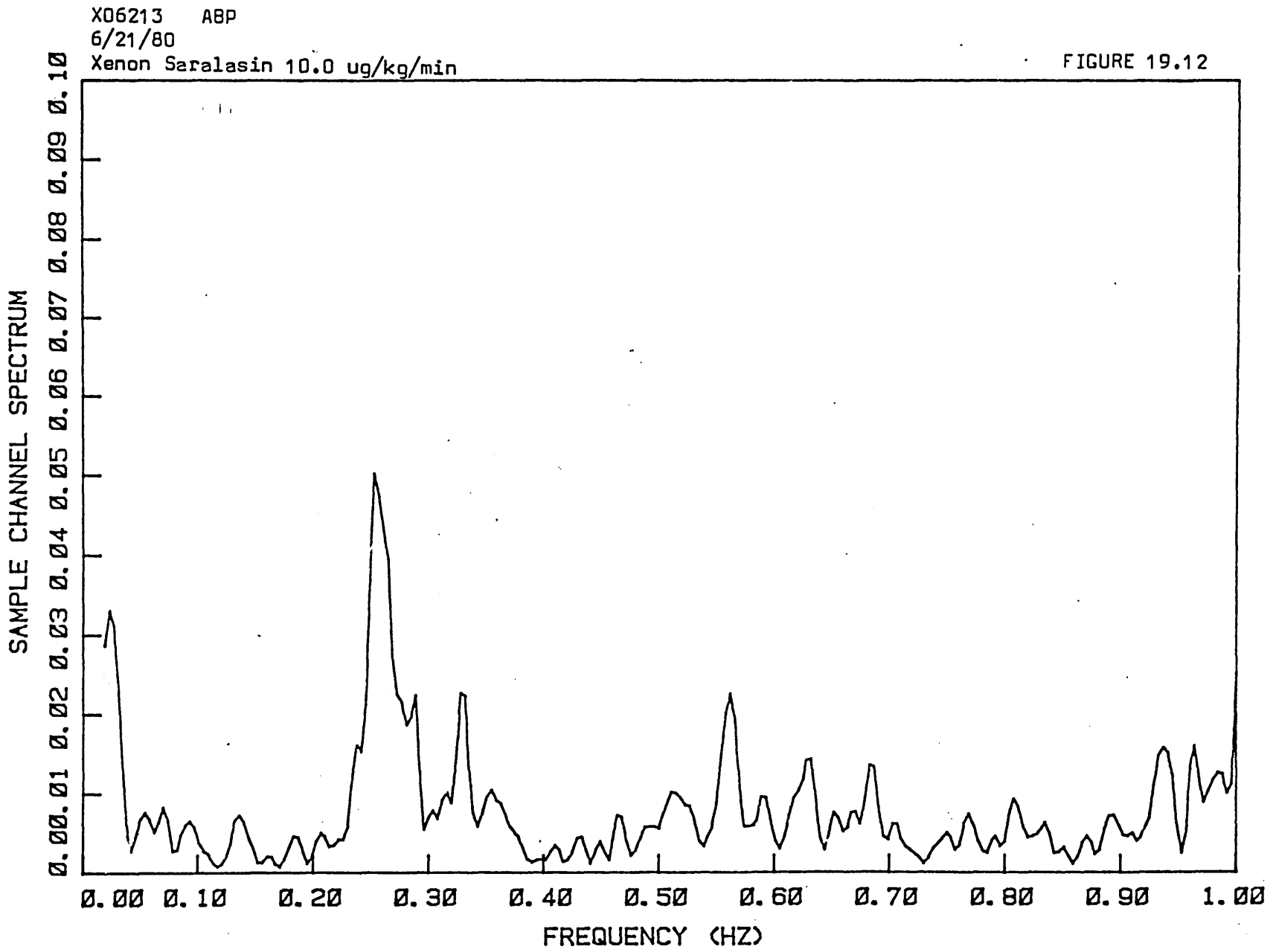

X06213
6/21/80
Xenon Saralasin 10.0 ug/kg/min
FIGURE 19.07
INSTANTANEOUS HEART-RATE FLUCTUATIONS SPECTRUM
0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.10
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)

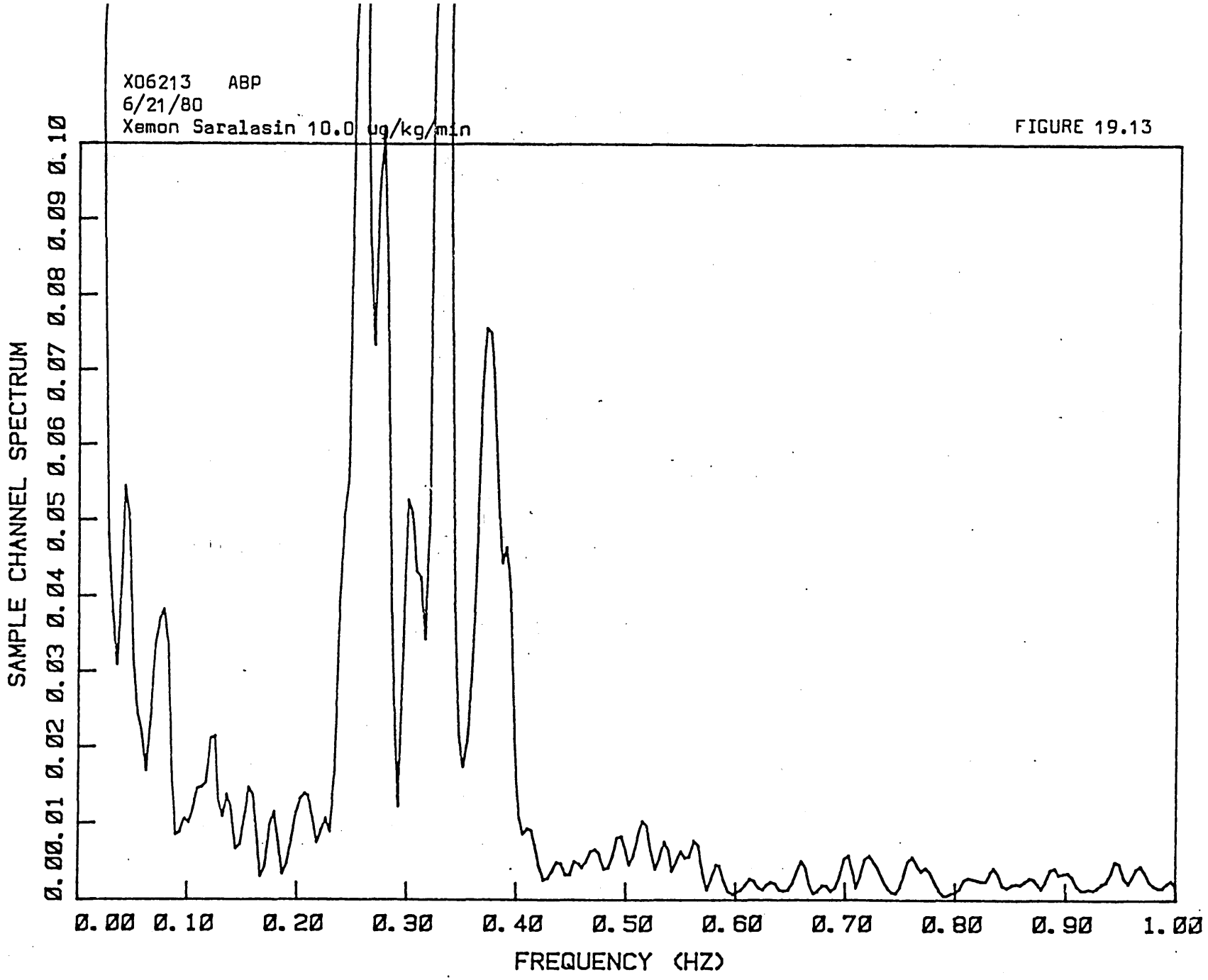

X06210 ABP
6/21/80
Xenon No Drug
FIGURE 19.08
SAMPLE CHANNEL SPECTRUM
0.02
0.01
0.00
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)


X06211 ABP
6/21/80
Xenon Saralasin 1.0 ug/kg/min
FIGURE 19.09
SAMPLE CHANNEL SPECTRUM
0.02
0.01
0.00
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)


X06212 ABP
6/21/80
Xenon Saralasin 5.0ug/kg/min
FIGURE 19.10
SAMPLE CHANNEL SPECTRUM
0.02
0.01
0.00
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)


X06212 ABP
6/21/80
Xenon Saralasin 5.0 ug/kg/min
FIGURE 19.11
SAMPLE CHANNEL SPECTRUM
0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.10
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)


X06213 ABP
6/21/80
Xenon Saralasin 10.0 ug/kg/min
FIGURE 19.12
SAMPLE CHANNEL SPECTRUM
0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.10
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)


X06213 ABP
6/21/80
Xemon Saralasin 10.0 ug/kg/min
FIGURE 19.13
SAMPLE CHANNEL SPECTRUM
0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.10
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)

DOG: XENON

DATE OF EXPERIMENT: July 1,1980

BASELINE

DRUG : NONE

INTERVENTION #1

DRUG: Converting Enzyme Inhibitor

INTERVENTION #2

DRUG

INTERVENTION #3

DRUG

INTEGRATED AREAS OF SPECTRAL PEAKS

RUN	CHANNEL ANALYZED	LOW FREQ. PEAK	MID FREQ. PEAK	HIGH FREQ. PEAK
Baseline	HR	1.59 E-3	2.46 E-3	2.13 E-2
	A_0P	1.03 E-4	1.55 E-4	1.74 E-3
	Resp	1.37 E-3	1.13 E-3	1.11 E-2
INT. #1	HR	.271 E-3	1.14 E-3	1.94 E-2
	A_0P	.897 E-4	1.16 E-4	1.38 E-3
	Resp	1.42 E-3	1.38 E-3	2.00 E-2
INT. #2				
INT. #3				

FIGURE 20.1

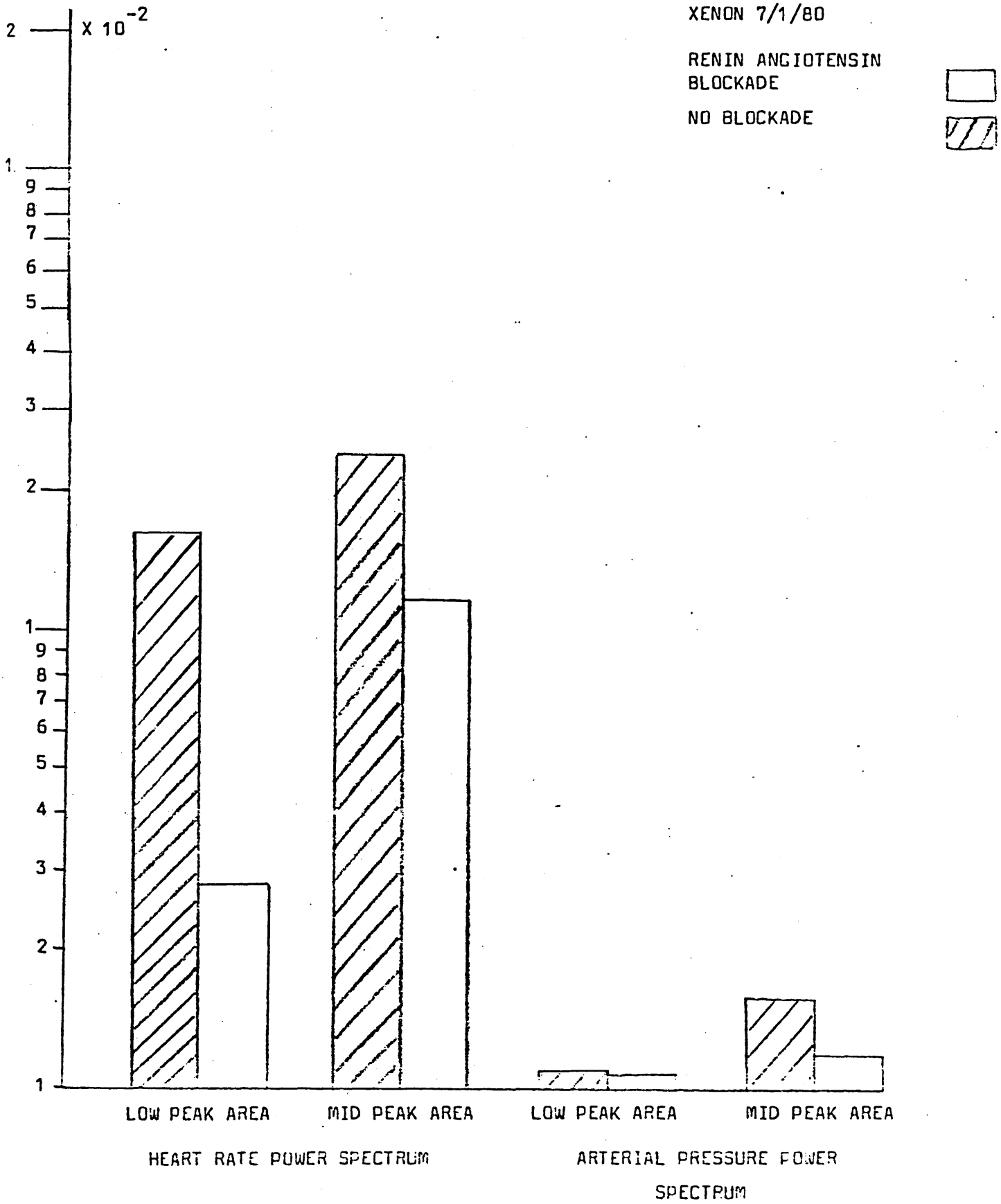
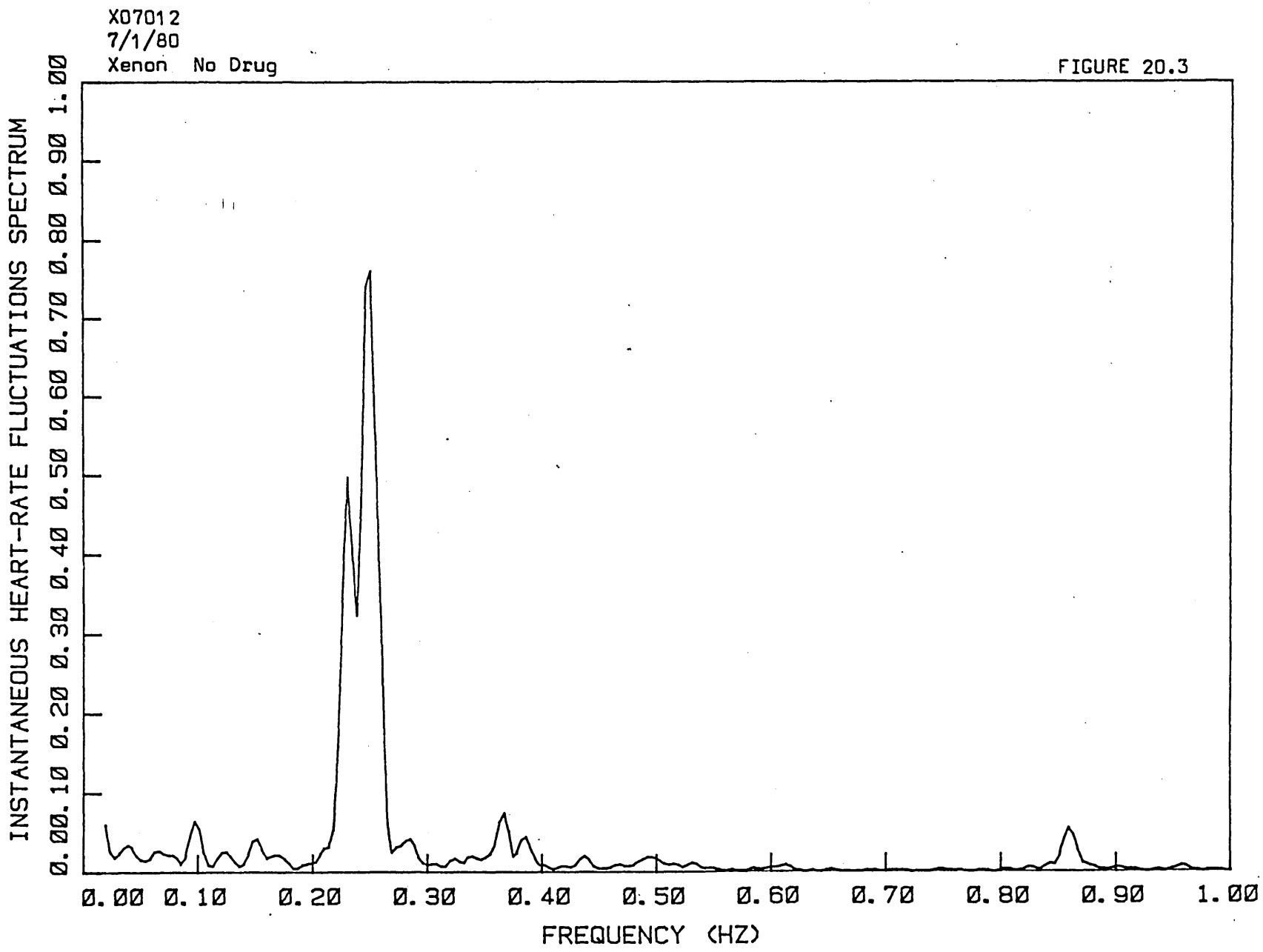
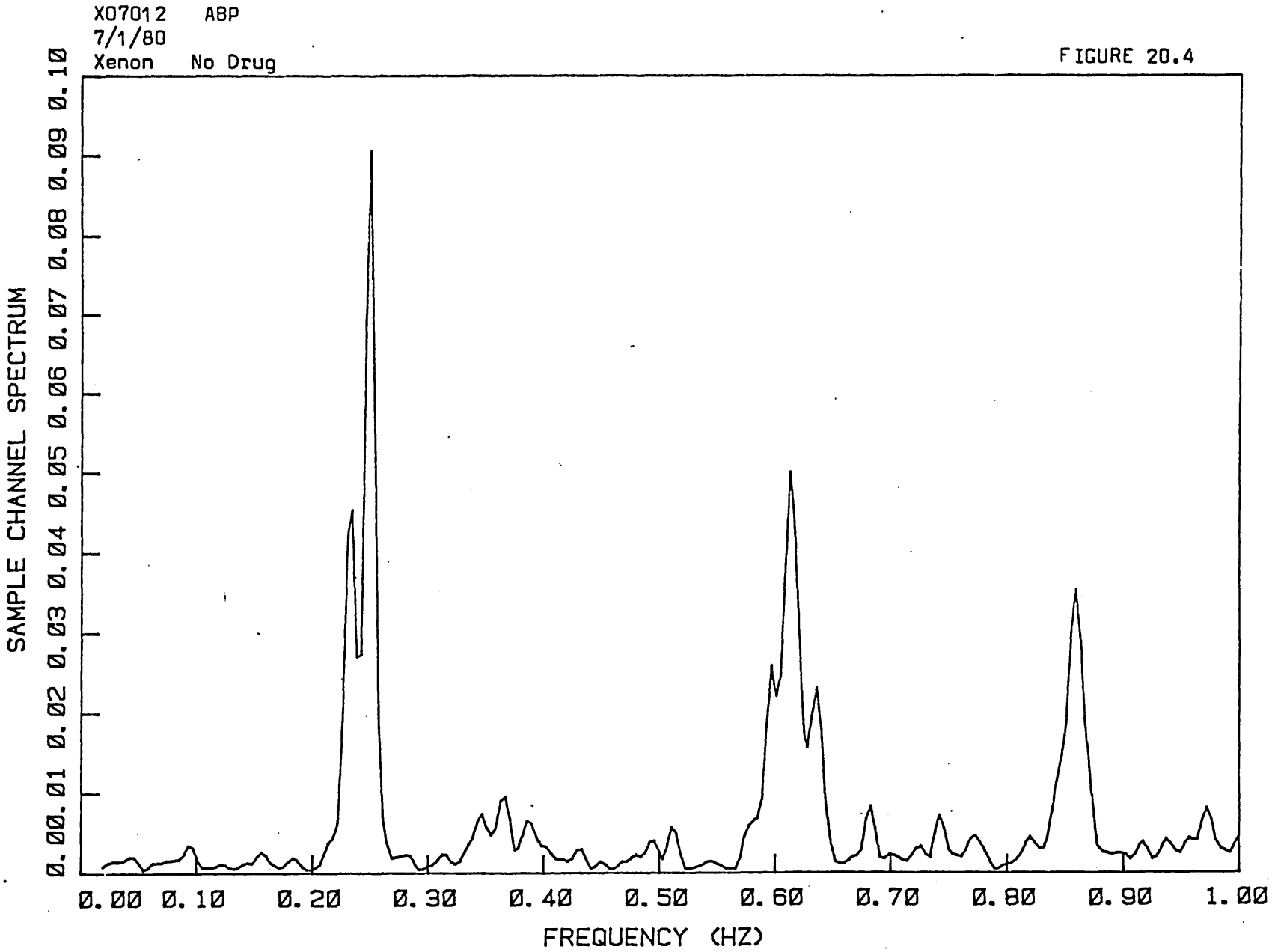
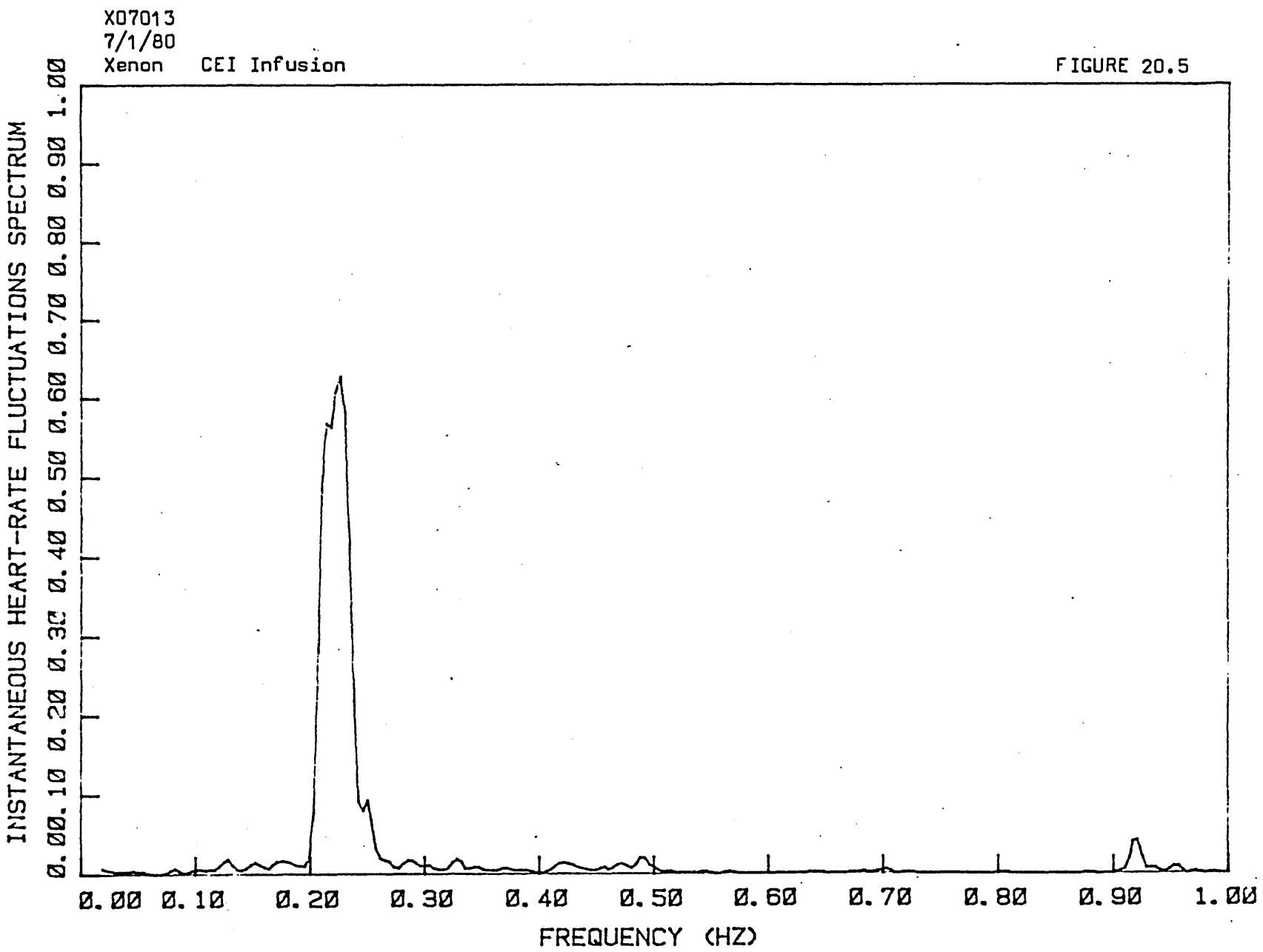
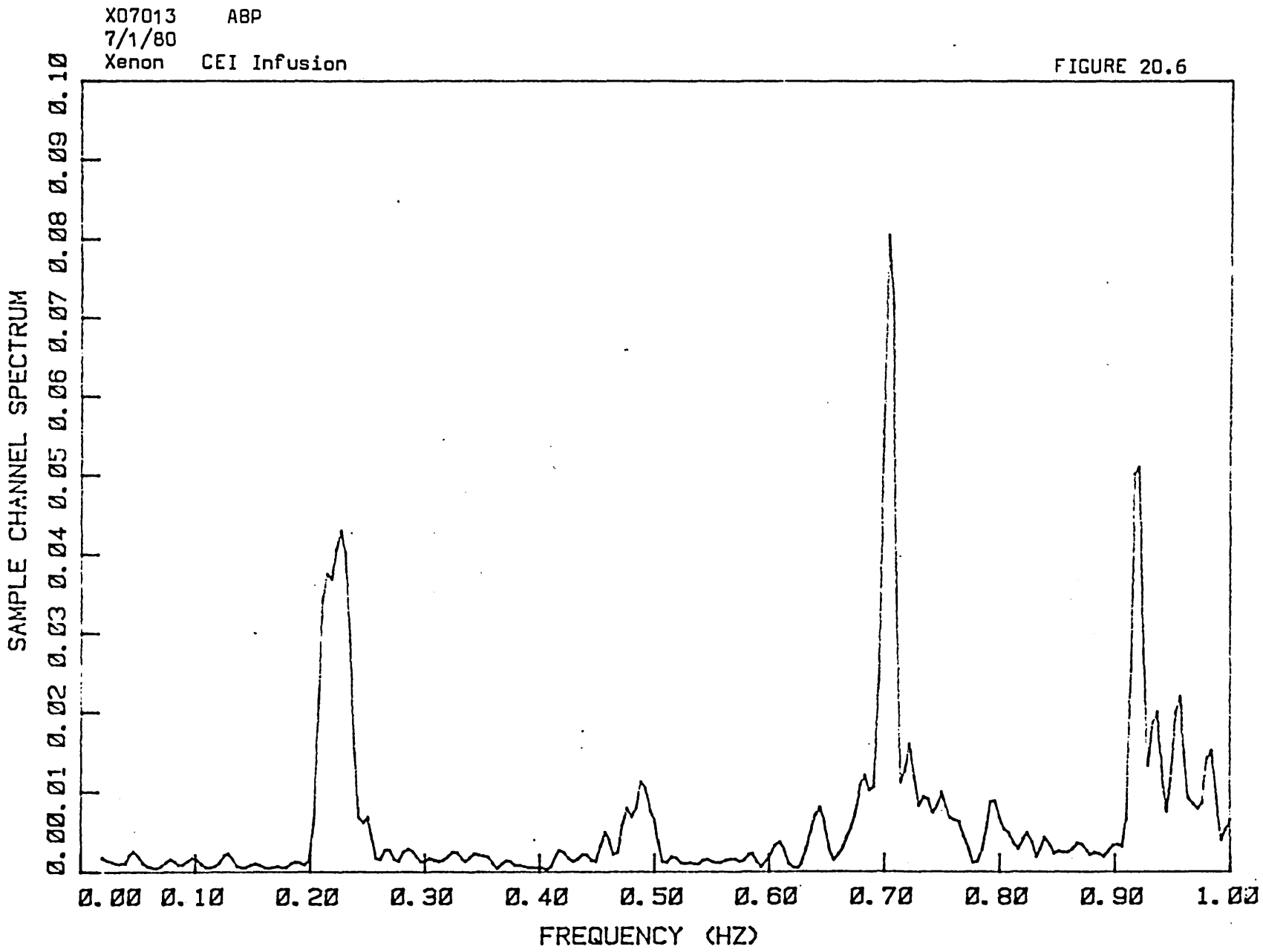

XENON 7/1/80
RENIN ANGIOTENSIN BLOCKADE
NO BLOCKADE
X 10^-2
2
1
9
8
7
6
5
4
3
2
1
9
8
7
6
5
4
3
2
1
LOW PEAK AREA
MID PEAK AREA
LOW PEAK AREA
MID PEAK AREA
HEART RATE POWER SPECTRUM
ARTERIAL PRESSURE POWER SPECTRUM

FIGURE 20.2


X07012
7/1/80
Xenon No Drug
FIGURE 20.3
INSTANTANEOUS HEART-RATE FLUCTUATIONS SPECTRUM
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)


X07012 ABP
7/1/80
Xenon No Drug
FIGURE 20.4
SAMPLE CHANNEL SPECTRUM
0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.10
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)


X07013
7/1/80
Xenon CEI Infusion
FIGURE 20.5
INSTANTANEOUS HEART-RATE FLUCTUATIONS SPECTRUM
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)


X07013 ABP
7/1/80
Xenon CEI Infusion
FIGURE 20.6
SAMPLE CHANNEL SPECTRUM
0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.10
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)

DOG: Volta

DATE OF EXPERIMENT: August 12,1980

BASELINE

DRUG : NONE

INTERVENTION #1

DRUG: Converting Enzyme Inhibitor

INTERVENTION #2

DRUG

INTERVENTION #3

DRUG

INTEGRATED AREAS OF SPECTRAL PEAKS

RUN	CHANNEL ANALYZED	LOW FREQ. PEAK	MID FREQ. PEAK	HIGH FREQ. PEAK
Baseline	HR	1.586 E-4	2.318 E-4	.9392 E-4
	A_oP	0.558 E-4	0.500 E-4	0.3696 E-4
INT. #1	HR	1.936 E-4	4.425 E-4	6.647 E-4
	A_oP	0.661 E-4	0.652 E-4	0.557 E-4
INT. #2				
INT. #3				

FIGURE 21.1

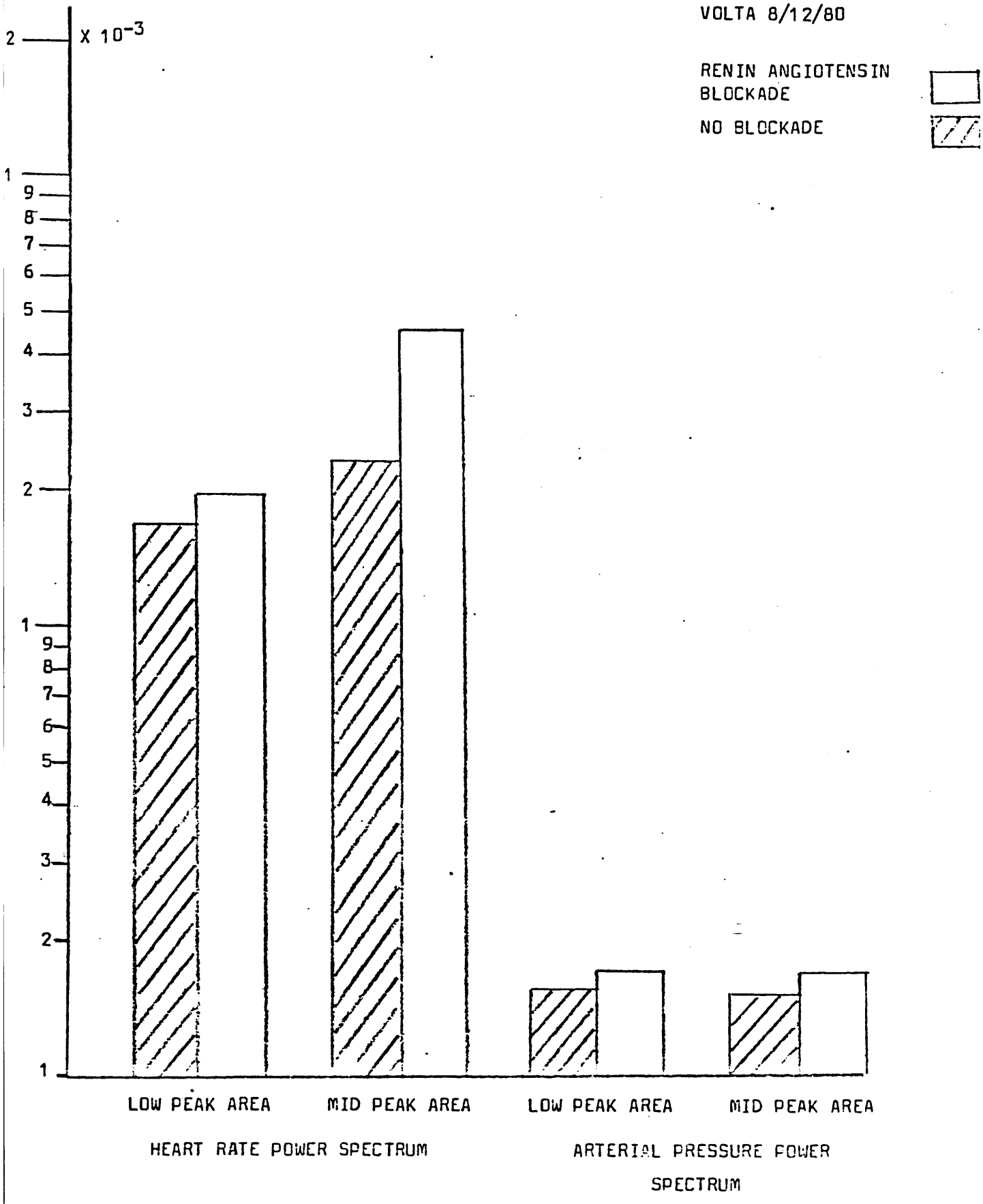

VOLTA 8/12/80
RENIN ANGIOTENSIN BLOCKADE
NO BLOCKADE
X 10-3
2
1
9
8
7
6
5
4
3
2
1
9
8
7
6
5
4
3
2
1
LOW PEAK AREA
MID PEAK AREA
LOW PEAK AREA
MID PEAK AREA
HEART RATE POWER SPECTRUM
ARTERIAL PRESSURE POWER SPECTRUM

FIGURE 21.2

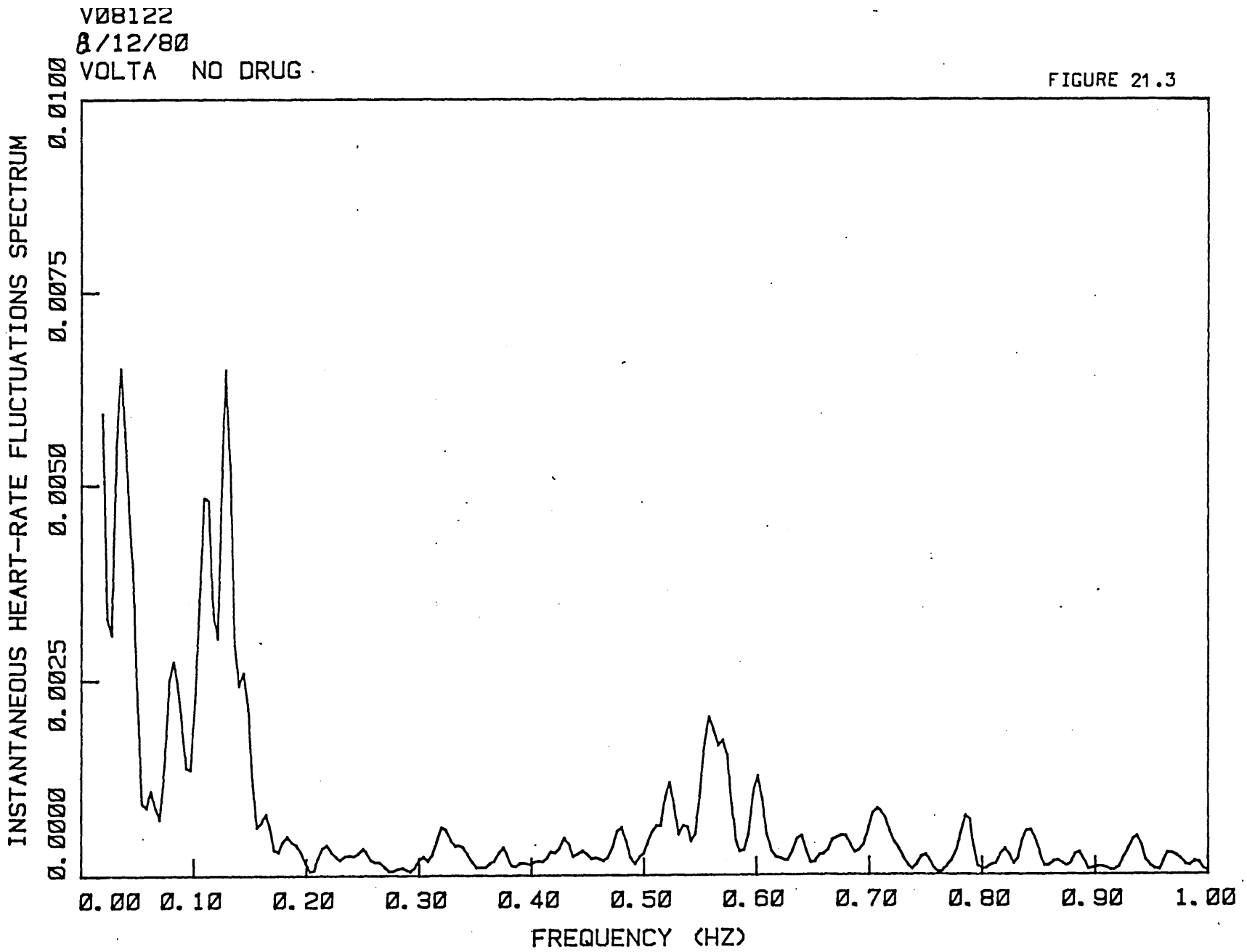
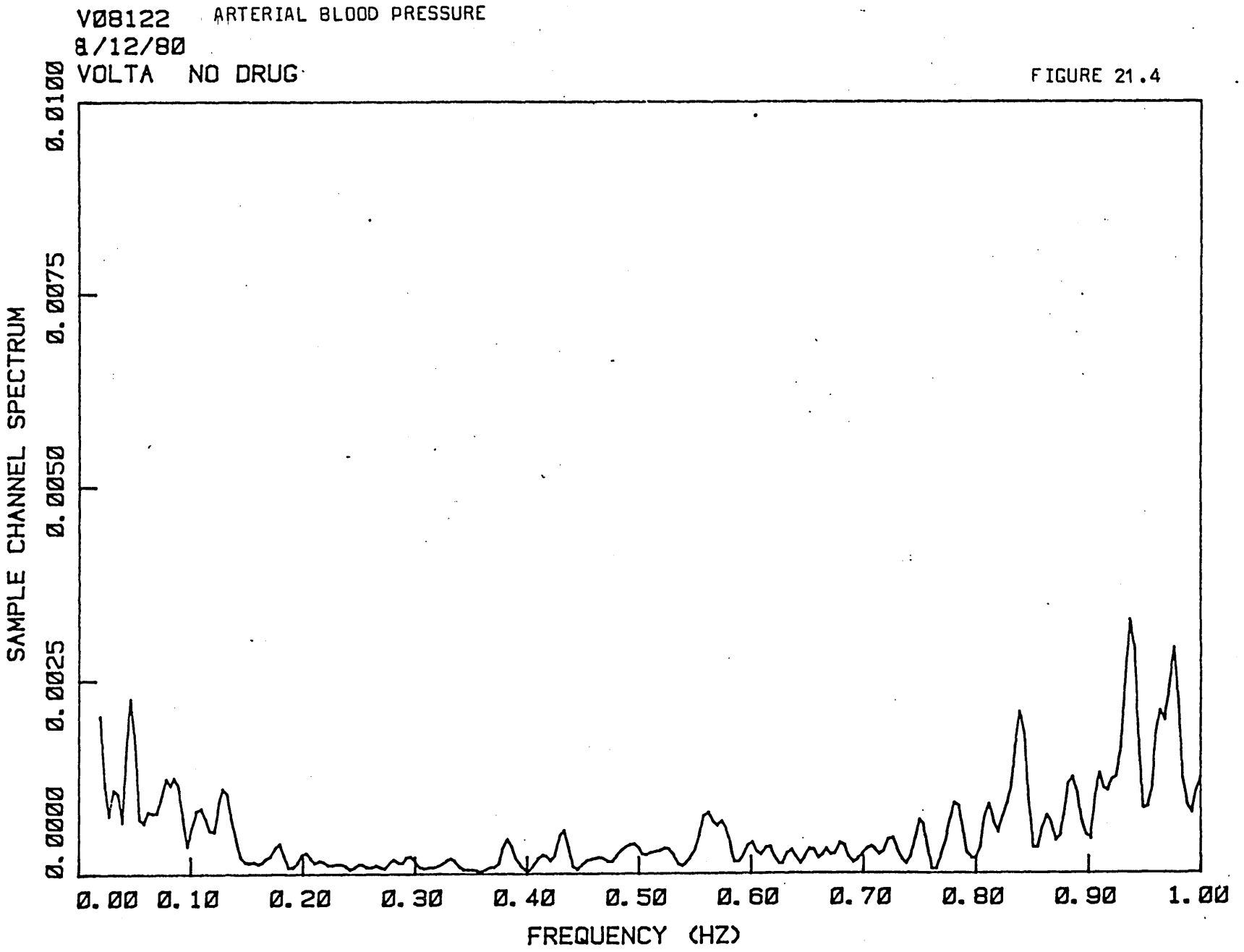

V08122
8/12/80
VOLTA NO DRUG
INSTANTANEOUS HEART-RATE FLUCTUATIONS SPECTRUM
0.0000
0.0025
0.0050
0.0075
0.0100
0.00
0.10
0.20
0.30
0.40
0.50
0.60
0.70
0.80
0.90
1.00
FREQUENCY (HZ)

FIGURE 21.3


V08122 ARTERIAL BLOOD PRESSURE
8/12/80
VOLTA NO DRUG
FIGURE 21.4
SAMPLE CHANNEL SPECTRUM
0.0100
0.0075
0.0050
0.0025
0.0000
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)

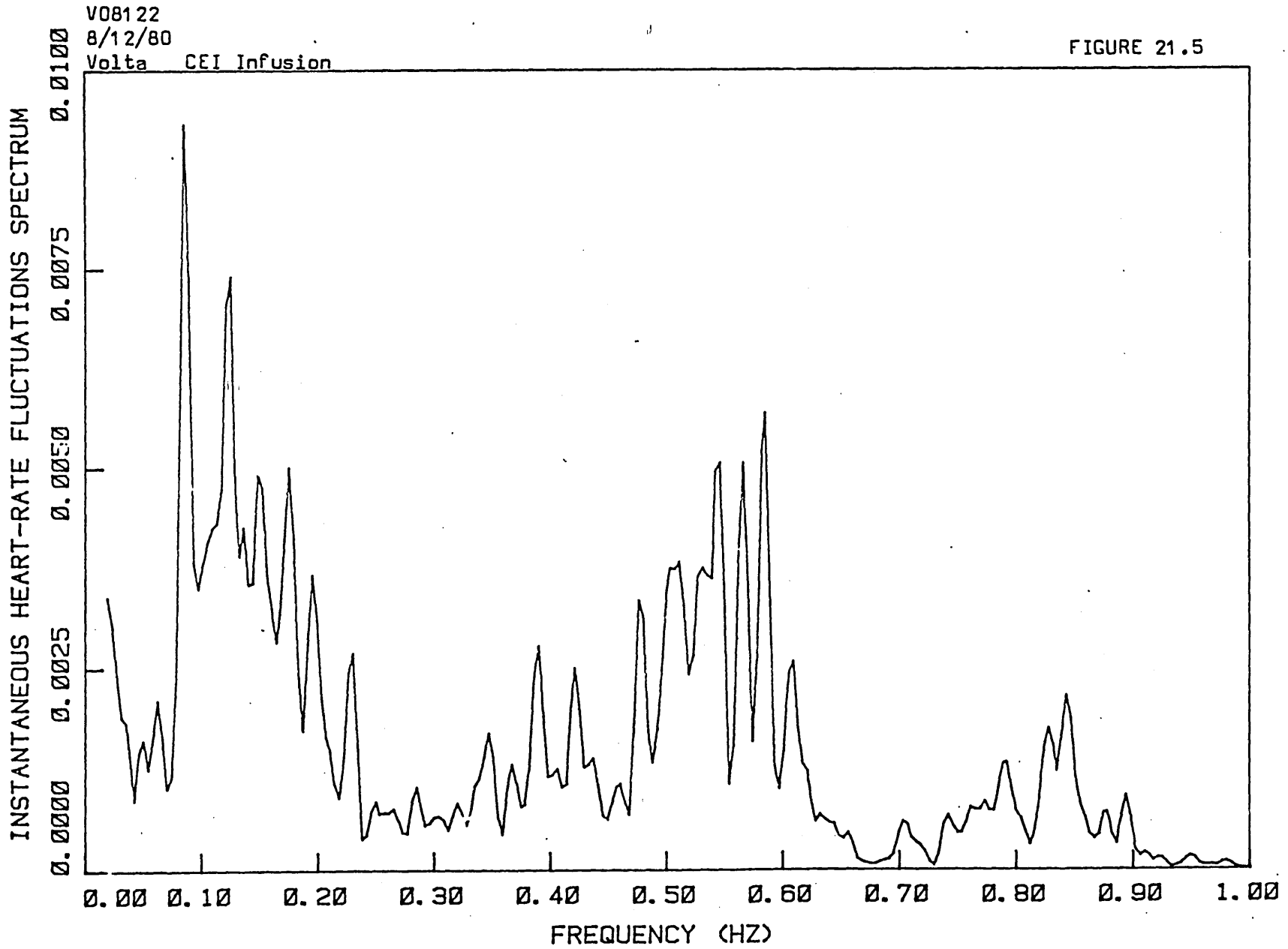
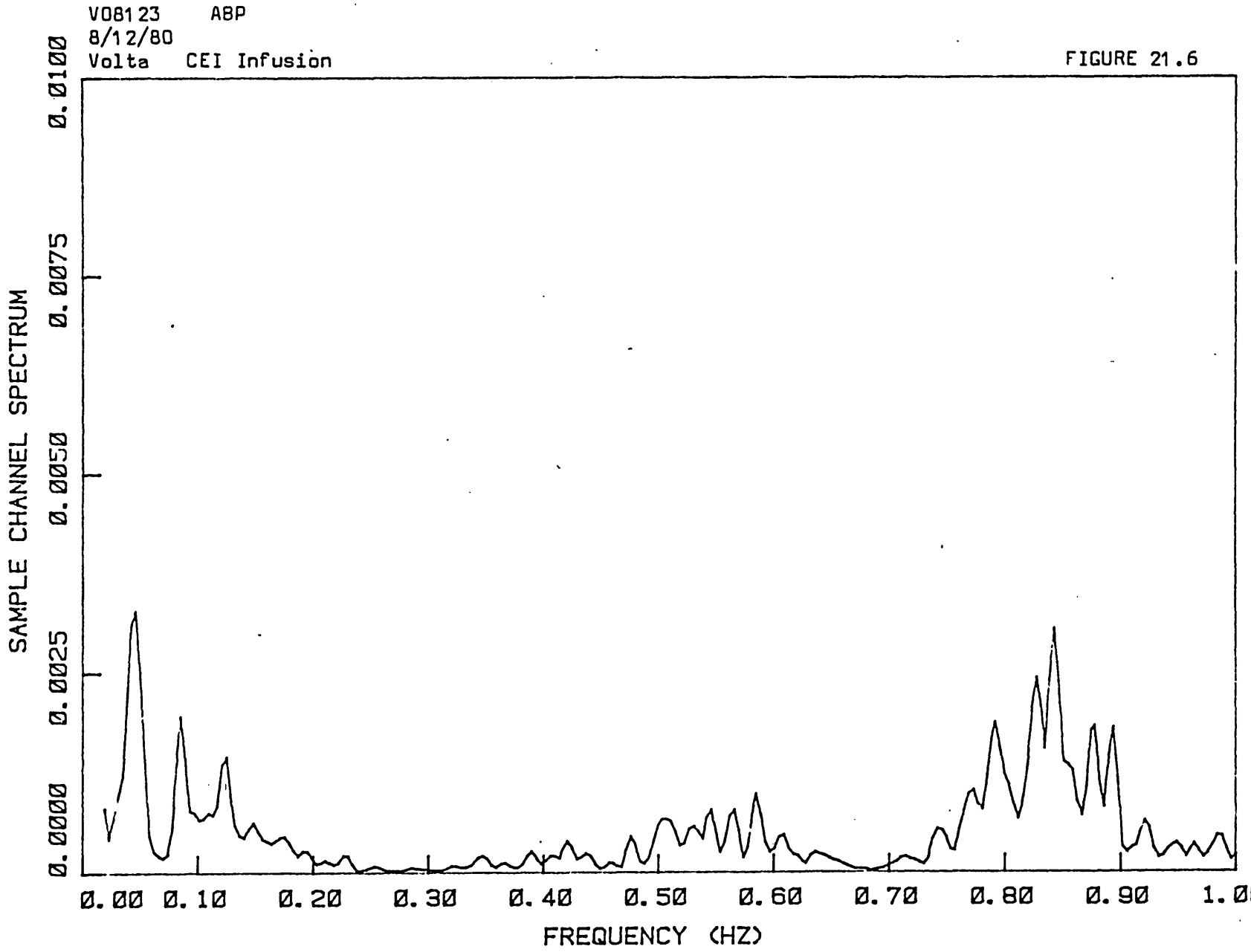

V08122
8/12/80
Volta CEI Infusion
INSTANTANEOUS HEART-RATE FLUCTUATIONS SPECTRUM
0.0000
0.0025
0.0050
0.0075
0.0100
0.00
0.10
0.20
0.30
0.40
0.50
0.60
0.70
0.80
0.90
1.00
FREQUENCY (HZ)

FIGURE 21.5


V08123 ABP
8/12/80
Volta CEI Infusion
FIGURE 21.6
SAMPLE CHANNEL SPECTRUM
0.0100
0.0075
0.0050
0.0025
0.0000
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
FREQUENCY (HZ)

```
% file: LEXI
%       Lexical processing routines
%       P. Schlueter  5 August 1980

RADIX @ DECIMAL

13      'EOL CONSTANT           % line seperator character (CR)
12      'EOP CONSTANT           % end-of-page character (↑L)
09      'HT  CONSTANT           % tab
32      'HS  CONSTANT           % space

% (EOL?) detects end-of-file (EOF), end-of-page (EOP),
%         and end-of-line (EOL) characters.
%         On return, (FLAGS):  0 if not terminator
.  ASSEMBLER<
  B PUSH,  1 C MVI,
    EOF CPI,  IFNZ,  0 C MVI,  THEN,
    EOP CPI,  IFNZ,  0 C MVI,  THEN,
    EOL CPI,  IFNZ,  0 C MVI,  THEN,
  C DCR,  B POP,  RET,  >
'(EOL?) CONSTANT

% buffer-address GETLINE
% read line of text from disk to textbuf, in STOIC string format
% zero length string means end-of-file
'GETLINE  CODE<  H POP,  H PUSH,  H INX,  0 D LXI,
  .  H PUSH,  D PUSH,  (GETBYTE) CALL,  D POP,  H POP,
     A M MOV,  H INX,  D INX,  (EOL?) CALL,  JZ,
  EOF CPI,  IFNZ,  0 D LXI,  THEN,
  H POP,  E M MOV,  NEXT JMP,  >

% (TOK?) detects end-of-file (EOF), end-of-page (EOP),
%        space, tab, and end-of-line (EOL) characters.
%        On return, (FLAGS):  0 if not token separator.
.  ASSEMBLER<
  B PUSH,  1 C MVI,
    HT  CPI,  IFNZ,  0 C MVI,  THEN,
    HS  CPI,  IFNZ,  0 C MVI,  THEN,
    EOF CPI,  IFNZ,  0 C MVI,  THEN,
    EOP CPI,  IFNZ,  0 C MVI,  THEN,
    EOL CPI,  IFNZ,  0 C MVI,  THEN,
  C DCR,  B POP,  RET,  >
'(TOK?) CONSTANT

% buffer-address TOKEN          Extracts first TOKEN from buffer.
%                               Pointer to token (STOIC string format)
%                               returned on stack.
'TOKEN CODE<
  H POP,  H PUSH,  H INX,  0 D LXI,
  .  M A MOV,  H INX,  D INX,  (TOK?) CALL,  JZ,
  H DCX,  0 M MVI,
  D DCX,  H POP,  H PUSH,  E M MOV,  NEXT JMP,  >

RADIX !
:F
```

FIGURE 22

```
% file: GRAPH
%       General graphics utilities.
%       P. S. Schluter  4 August 1980

% General graphics utilities.

RADIX @ DECIMAL

0       'XLEFT  VARIABLE        % define graph size
1000    'XSPAN  VARIABLE
0       'YLOW   VARIABLE
700     'YSPAN  VARIABLE
1       'NDP    VARIABLE        % number of digits after decimal point
() <#>  'XNFMT  VARIABLE        % address of INTEGER formatting routine
                                % for axis numbering.

15      'TKSIZE CONSTANT        % length of tick mark

% Draw box around plot area
'PBOX :
  XLEFT @ YLOW @ MOVE
  XLEFT @ XSPAN @ + YLOW @ DRAW
  XLEFT @ XSPAN @ + YLOW @ YSPAN @ + DRAW
  XLEFT @ YLOW @ YSPAN @ + DRAW
  XLEFT @ YLOW @ DRAW
;

% Draw tick upwards (for X-axis)
'TKU : DDUP MOVE TKSIZE + DRAW ;

% Draw tick to the right (for Y-axis)
'TKR : DDUP MOVE SWAP TKSIZE + SWAP DRAW ;

% N XTICKS  Draw N intervals along X-axis
'XTICKS :
  DUP 1+ 0 DO DUP XSPAN @ I FLIP */ XLEFT @ + YLOW @ TKU LOOP DROP ;

% N YTICKS  Draw N intervals along Y-axis
'YTICKS :
  DUP 1+ 0 DO DUP YSPAN @ I FLIP */ YLOW @ + XLEFT @ SWAP TKR LOOP DROP ;

% I DP<#>  Convert integer I to string with (NDP) digits after ".",
%          and at least one leading digit.
%          Example:  12345 DP<#> TYPE produces 123.45 if (NDP) = 2.
'DP<#> : <# NDP @ ( # ) "." 1+ BO #PUT #S #> ;

% X0 XI N XNUMBER  Number X-axis:  first value X0, increment XI, N intervals.
'XNUMBER :
  2SWAP DUP 1+ 0
  DO
    DUP XSPAN @ I FLIP */ XLEFT @ + YLOW @ 15 -
    3OVER I IF 5 ELSE 6 THEN SWAP XNFMT @ EXEC CHTYPE
    +ROT OVER + -ROT
  LOOP
  3DROP ;

% Y0 YI N YNUMBER  Number Y-axis:  first value Y0, increment YI, N intervals.
'YNUMBER :
  1 CHANGLE!
  2SWAP DUP 1+ 0
  DO
    DUP YSPAN @ I FLIP */ YLOW @ + XLEFT @ 15 - SWAP
```

```
    3OVER I IF 1 ELSE 0 THEN SWAP XNFMT @ EXEC CHTYPE
    +ROT OVER + -ROT
  LOOP
  3DROP
  0 CHANGLE!
;

% "X-axis string" XLABEL
'XLABEL : XSPAN @ 2/ XLEFT @ + YLOW @ 50 - 5 3OVER CHMSG DROP ;

% "Y-axis string" YLABEL
'YLABEL :
  1 CHANGLE!
  YSPAN @ 2/ YLOW @ + XLEFT @ 50 - SWAP 1 3OVER CHMSG DROP
  0 CHANGLE!
;

RADIX !
;F
```

```
% file: PWRPLT
%       Plot power spectrum from ASCII floating point file
%       P. S. Schluter  4 August 1980

% File format:
%
% line 1        AGNUS 7/25/80 : BASE    free text for plot title
% line 2        122.436 BPM             mean heart rate
% line 3        492.089 RR              mean R-R interval
% line 4        35.8649 SD              variance
% line 5        .389737 SKEW            skew
% line 6        1.49085 KURT            kurtosis
% line 7        0. BP                   blood pressure
% line 8        2.03215E-2 DF           delta-frequency
% line 9        51 NPTS                 number of spectrum values
% line 10       1.82E-2                 first spectrum value
%  etc
%  etc
%               <EOF>

RADIX @ DECIMAL

41      'RDBUF ARRAY            % read buffer for GETLINE

3       'PSPAN VARIABLE         % span (and number of ticks) of Y-axis,
                                % in 0.01 "power units"
0.0     'DELF FVARIABLE         % delta-frequency
0       'NVALS VARIABLE         % number of power spectrum values


% VIEW  Move plotter pen out of the way for viewing
'VIEW : XLEFT @ XSPAN @ +  YLOW @ YSPAN @ +  MOVE ;

% Plot labelled axis for power spectrum plot.
'PSBOX :
  DECIMAL
  () DP<#> XNFMT !              % axis numbered as decimal integers
  PBOX
  10 XTICKS                     % tick, number, and label X-axis
  1 NDP !  0 1 10 XNUMBER       %  0 (0.1) 1.0 Hertz
  "FREQUENCY (HZ)" XLABEL
  PSPAN @ YTICKS                % tick, number, and label Y-axis
  2 NDP !  0 1 PSPAN @ YNUMBER  %  0 (0.01) 0.01*PSPAN
  "R-R INTERVAL POWER SPECTRUM" YLABEL
;

% Scale floating point (frequency,power) for plotting.
% F-freq F-power FPSCALE X Y
'FPSCALE :
  PSPAN @ FLOAT 0.01 F* F/ YSPAN @ FLOAT F* INTEGER YLOW @ +
  +ROT
  1.0 F/ XSPAN @ FLOAT F* INTEGER XLEFT @ +
  SWAP
;

% Plot power spectrum for currently open file.
'PWRPLT :
  0 0 SPOS                      % position to beginning of file
  7 ( RDBUF GETLINE )           % skip to delta-frequency
  RDBUF GETLINE RDBUF TOKEN     % read in delta-frequency
  FLITERAL  NOT IF "DELTA-FREQUENCY NOT A FP NUMBER" ERR THEN  DELF F!
  RDBUF GETLINE RDBUF TOKEN     % read in number of data points
```

```
  ILITERAL  NOT IF "NVALS NOT AN INTEGER" ERR THEN  NVALS !
  0. 0. FPSCALE MOVE
  1. DELF F@ F/ INTEGER NVALS @ MIN 0
  DO
    I FLOAT DELF F@ F*  % frequency (abcissa)
    RDBUF GETLINE RDBUF TOKEN    % power (ordinate)
    FLITERAL  NOT IF "POWER NOT A FP NUMBER" ERR THEN
    FPSCALE DRAW
  LOOP
  VIEW
;

% Plot plot identification on top of box
'PSTITLE :
  0 0 SPOS
  RDBUF GETLINE                  % read in header text
  RDBUF B@ 1- RDBUF B!           % delete carriage return from string
  XLEFT @  YLOW @ YSPAN @ + 20 +  0
  RDBUF CHMSG
;

RADIX !
:F
```

```
% FILE : VARHIS
% WILL COMPUTE RRVAR (VARIANCE FROM RR-INTERVALS)
%  AND FROM INTEGRAL OF SPECTRUM
% WILL COMPUTE HISTOGRAM FROM THE RR-INTERVAL ARRAY AT EQUAL TIME INTERVALS

RADIX @ DECIMAL
0.0 'SIGMA FVARIABLE            % STANDARD DEVIATION
0.0 'RRVAR FVARIABLE            % VARIANCE OF RR-FLUCTUATIONS FROM NCTARRAY
0.0 'INTPOW FVARIABLE           % TOTAL POWER UNDER POWER SPECTRUM

0 'HIST2RG VARIABLE             % EXP OF HIGHEST POWER OF 2 FITTING IN 4*SIGMA
0 'HISTRANGE VARIABLE           % RANGE OF HIST AS LOWEST 2POWER LARGER
0 'HISTMAX VARIABLE             % MAX VALUE OF HISTOGRAM
                                % THAN 4*SIGMA
1 'HISIGN VARIABLE              % IS 1 WHEN RR AT RIGHT OF AVERAGE
                                % IS -1  "  "   " LEFT  "    "
0 'BINWID VARIABLE              % BINWIDTH FOR HISTOGRAM

64 'NBINS CONSTANT              % # BINS IN HISTOGRAM

NBINS 'HISTAR ARRAY             % ARRAY OF HISTOGRAM ,64. LENGTH


'ARVAR :
  ARLEN ! ARADR !
 0.E0 RRVAR F!
  ARLEN @ 0 DO ARADR @ I 2* + @ FLOAT DDUP F*
               RRVAR F@ F+ RRVAR F! LOOP
  RRVAR F@ CTPOW @ FLOAT F/ DDUP RRVAR F! "RRVAR=" MSG F=
;

'TOTPOW :
  0.E0 INTPOW F!
  CTPOW @ 2/ 0 DO FOO I 4 * + F@ INTPOW F@ F+ INTPOW F! LOOP
  INTPOW F@ FREDEL F@ F* CTAVER @ FLOAT DDUP F* F*
                       % necessary since spectrum has been divided by CTAVER↑2
                       % if not total power would not =variance
 DDUP INTPOW F! "INTPOW=" MSG F=
;


% ????? has instead the variance to be divided by CTAVER↑2 . ???
% ????? has width of histogram to be normalized by CTAVER↑2

'HISTGRAM :
  ARLEN ! ARADR !                       % store address and length
  ARADR @ ARLEN @ ARVAR
  RRVAR F@ FSQRT DDUP SIGMA F!
               4.E0 F*                  % 4 standard deviations
               FLOG2 INTEGER HIST2RG !          % lowest exp of 2 fitting
                                                % in 4*sigma
  2 HIST2RG @ 0 DO 2* LOOP HISTRANGE !          % twice lowest 2 power
                                                % contained in 4*sigma
  HISTRANGE @ NBINS / BINWID !          % histrange divided in 64.=40H bins
1 HISIGN !
  ARLEN @ 0 DO ARADR @ I 2* + @
               DUP LTZ IF -1 HISIGN !
               THEN ABS BINWID @ / NBINS 2/ MIN
               HISIGN @ *
               2* HISTAR + NBINS 2/ + 1+!
            1 HISIGN !
       LOOP
```

```
;

'HISTBOX :
  DECIMAL
  () DP<#> XNFMT !
  PBOX
  8 XTICKS
  2 NDP ! 0 HISTRANGE @ 100 8 */ 8 XNUMBER
  "TIME (MSEC)" XLABEL
  4 YTICKS
  2 NDP ! 0
          HISTMAX @ FLOAT CTPOW @ FLOAT F/ 100 FLOAT F* 4 FLOAT F/ INTEGER
          4 YNUMBER
  "HISTOGRAM" YLABEL
;


'HISTPLOT :
  CTARRAY CTPOW @ HISTGRAM
  RRVAR F@ "RRVAR=" MSG F=
  SIGMA F@ "SIGMA=" MSG F=
  HISTAR NBINS ARMAX
  MAXVAL @ HISTMAX !
  HISTBOX
  HISTAR NBINS IGRPLOT

;


RADIX !
:F
```

```
% FILE : RRSP
%       ROUTINES FOR STORING RR INTERVALS OUT OF TWAVE DISK DATA
%       INTO AN ARRAY AND ANALYZING THIS ARRAY

RADIX @ DECIMAL

90 'TINT VARIABLE               % TIME INTERVAL BETWEEN INTERPOLATED RR-INT
0 'BPOS VARIABLE                % DISK POSITION (FIRST BYTE OF BLOCK)
0 'NBYTES VARIABLE              % NUMBER OF BYTES IN BLOCK
0 'PUTPTR VARIABLE              % POINTER TO ADDRESS IN RRARRAY
0 'RRCOUNT VARIABLE             % COUNTER TO CARDIAC BLOCKS ON FILE
0 'CTCOUNT VARIABLE             % COUNTER TO # RRSAMPLES AT EQUAL TIME INT
0 'RREM VARIABLE                % REMAINDER OF DIV BY TINT FOR INTERPOLATION
0 'RRHIGH VARIABLE              % HIGH CUTOFF FOR DECIDING IF BAD POINT
0 'RRLOW VARIABLE               % LOW    "     "      "    "   "   "
0 'RRAVER VARIABLE              % AVERAGE RR-INTERVAL
                                % OF RRVALUES AT EQUAL TIME INTERVALS
0 'CURR VARIABLE                % CURRENT RR VALUE
0 'CTPTR VARIABLE               % PUTPOINTER IN CTARRAY
0 'QUOT VARIABLE                % # RRVALUES TO BE STORED IN CTARRAY
0 'CT2LN VARIABLE               % LOG2 ARRAY LENGTH FOR FFT
0 'CTPOW VARIABLE               % ARRAY LENGTH FOR FFT

0 'ARADR VARIABLE               % ADDRESS FOR ARRAY TO BE PLOTTED
0 'ARLEN VARIABLE               % LENGTH   "   "     "  "     "
0 'XEND VARIABLE                % HIGHER LIMIT FOR X-AXIS ON PLOT
0 'YEND VARIABLE                %    "     "    "  Y  "    "   "
0 'MAXVAL VARIABLE              % MAX VALUE OF VARIABLE ARRAY
0 'MINVAL VARIABLE              % MIN   "   "       "      "
0 'CTAVER VARIABLE              % AVERAGE VALUE FOR CTARRAY
0.0 'HRAVER FVARIABLE           % NOT USED BY RRSP ,NECESSARY TO MAKE
0.0 'SMAVER FVARIABLE           % AVERAGE SAMPLE VALUE,  "     "   "
                                % RRFFT COMPATIBLE WITH SMMSP,RRSP AND HRSP
0 'SMCHAN VARIABLE              % CHANNEL # FOR SMPLE CHANNELS
0.0 'RESPSIG FVARIABLE          % ST DEVIATION FOR RESP SIGNAL
0.0 'TTAVER FVARIABLE           % AVERAGE TWAVE PARAM,FOR MULTIPLE USE
                                % OF RRFFT
0 'TPARAM VARIABLE              % INDEX FOR T-WAVE PARAM TO BE ANALYZED
                                % FOR MULTIPLE USE OF RRFFT
0 'PACEF VARIABLE               % PACING FREQ,FOR MULTIPLE USE OF RRFFT

0 'RRADR VARIABLE               % ADDRESS FOR RR-VALUE TO BE CORRECTED
0 'RRVAL VARIABLE               % NEW VALUE "     "     "  "     "

0.0 'CTSLOPE FVARIABLE          % SLOPE OF CTARRAY FROM LSQ FIT
0.0 'CCEPT FVARIABLE            % INTERCEPT OF LINE FITTED TO CTARRAY
0.0 'FMAXVAL FVARIABLE          % MAX VALUE OF FLOATING PT ARRAY
0.0 'FREQMAX FVARIABLE          % MAX FREQUENCY IN SPECTRUM

360 'SFREQ CONSTANT             % SAMPLING RATE 360.=168H

8192 'FOOLEN CONSTANT           % ARRAY LENGTH FOO   (1024.*8)
3072 'CTLEN CONSTANT            %   "     "  CTARRAY(1024.*2)
FOOLEN 'FOO ARRAY               % ARRAY FOR FLOAT REAL AND IM RR VALUES
                                % WILL STORE ORIGINAL RRARRAY TOO
                                % WILL STORE POWER SPECTRUM IN 1024 *4
CTLEN 'CTARRAY ARRAY            % "      "  INTERPOLATED RR VALUES

4000 'NOBLK CONSTANT            % # BLOCKS TO READ THROUGH TO HAVE ENOUGH
                                % CARDIAC BLOCKS
```

```
'GETWORD : GETBYTE GETBYTE 256 * + ;

'GET# : RDLINE WORD DROP . ILITERAL
        EQZ IF "INVALID NUMBER" ERR THEN ;


'RREOF :                          % when EOF block is met stop file scan
"RRCOUNT=" MSG CR
  RRCOUNT @ U=
  CR " EOF BLOCK ENCOUNTERED " MSG
;


'PUTRR :                          % stores RR and resets pointer to array
  PUTPTR @ ! PUTPTR @ 2 + PUTPTR !
;


'RRQRS :                          % read QRS block ,no need for obs time and no
                                  % need for beat classification
  GETWORD GETWORD GETWORD 3DROP
  CR "RR  " MSG
                        % get and put the RR
  RRCOUNT @ 1 + RRCOUNT !
RRCOUNT @ 5 GE IF GETWORD DUP PUTRR U= THEN
;


'DDQRS :                          % routine for finding the cardiac blocks
  GPOS DROP BPOS !                % get position and store
  GETWORD                         % get the type word
  GETWORD NBYTES !                % get # bytes and store
  DUP 3 EQ IF RRQRS THEN          % check if QRS block (type=3)
  DUP 5 EQ IF RREOF THEN          % check if EOF  "    ( "  =5)
  DROP
  BPOS @ NBYTES @ + 0 SPOS        % if none of both set the pos at next block
;


'RSCAN :                          % main program to read and store RR
  1024 0 SPOS
  0 RRCOUNT !
  FOO PUTPTR !
  NCBLK 0 DO RRCOUNT @ 5 - CTLEN 2/ LT IF  DDQRS
                                       ELSE CR "RRCOUNR >1200" MSG EXIT
                                       THEN LOOP
;

'RRCORR :
0 0
  RRCOUNT @ 5 - 0 DO FOO I 2 * + @ M+ LOOP
  RRCOUNT @ 5 - UM/ DUP RRAVER ! CR "RRAVER=" MSG U= CR

  RRAVER @ FLOAT 1.6 F* INTEGER RRHIGH !
  RRAVER @ FLOAT .6 F* INTEGER RRLOW !
CR "POSSIBLE BAD POINTS" MSG
  RRCOUNT @ 5 - 0 DO FOO I 2* + @ DUP
                RRHIGH @ GE IF DUP CR = "AT I =" MSG I =
                               "   PRE: " MSG FOO I 1- 2* + @ =
                               "   AFT: " MSG FOO I 1+ 2* + @ =

           THEN DUP RRLOW @ LE IF DUP CR = "AT I=" MSG I =
                               "   PRE: " MSG FOO I 1- 2* + @ =
```

```
        THEN DROP LOOP
CR "ENTER CORRECTIONS IN FOO ARRAY OF RR-INTERVALS" MSG CR

25 0 DO "FIXPOINT?  " MSG
        GET#  DUP GTZ IF RRADR !
                                " ? " MSG GET# FOO RRADR @ 2* + !
                        ELSE EXIT THEN
        LOOP

20 0 DO "INSERT?  " MSG
        GET# DUP GTZ IF RRADR !
                                " ? " MSG GET# RRVAL !
                               RRCOUNT @ 5 - RRADR @ DO FOO I' 2* + @
                                                     FOO I' 1+ 2* + !
                                                LOOP
                % RRvalues from RRADR on, moved up by 1 address
                % new value will be inserted at FOO+RRADR
                % RRCOUNT to be incremented
                                RRVAL @ FOO RRADR @ 2* + !
                                RRCOUNT @ 1+ RRCOUNT !
                        ELSE EXIT THEN
        LOOP



20 0 DO "DELETE?  " MSG
        GET# DUP GTZ IF RRADR !
                               RRCOUNT @ 5 - 1- RRADR @ DO FOO I 1+ 2* + @
                                                     FOO I 2* + !
                                                LOOP
                % RRvalues from RRADR on ,moved back by 1 address
                % RRCOUNT to be decremented
                                        RRCOUNT @ 1- RRCOUNT !
                        ELSE EXIT THEN
        LOOP

CR " RR-ARRAY CORRECTED" MSG CR


;

% now the original RRarray is built up (in FOO)
% an equal time interval array CTARRAY will be computed
% the DC drift subtracted keeping the average RR constant
% and the average RR will be subtracted too



'FMAX : DOVER DOVER FLE IF DSWAP THEN 2DROP ;
'FMIN : DOVER DOVER FGE IF DSWAP THEN 2DROP ;

'CTPUT :
  CTPTR @ ! CTPTR @ 2 + CTPTR !         % stores the RR at equal time interval
;

'ARMAX :                        % has to be provided with array adress at top-1
                                %                          "   length at top
  CR
  DUP ARADR ! @         % copy address and get first value
  SWAP 1 DO ARADR @ I 2* + @ MAX LOOP MAXVAL !
;
```

```
:ARMIN :                        % has to be provided with array address at top-1
                                %                    "     length at top
  SWAP
  DUP ARADR ! @
  SWAP 1 DO ARADR @ I 2* + @ MIN LOOP MINVAL !
;


"LOADING SPSIZE" MSG CR

:SPSIZE :
  CTCOUNT @ FLOAT FLOG2 INTEGER CT2LN !
  1 CT2LN @ 0 DO 2* LOOP CTPOW !
  CR " # POINTS TO BE USED FOR FFT IS " MSG CTPOW @ U= CR
;

"LOADING AVCT" MSG CR


:AVCT :
  0 0
  CTPOW @ 0 DO CTARRAY I 2* + @ M+ LOOP
  CTPOW @ UM/ DUP CTAVER ! CR " CTAVER= " MSG U= CR
;

"LOADING RRFIT" MSG CR

:RRFIT :
                                                % fit CTARRAY to a straight line
  <LSQ
  CTPOW @ 0 DO TINT @ FLOAT I FLOAT F* SFREQ FLOAT F/
               CTARRAY I 2* + @ FLOAT
               LSQ LOOP
  LSQ> DDUP "SLOPE=" MSG F=
         CTSLOPE F!  CCEPT F!
;

"LOADING NEWCT" MSG CR

:NEWCT :
  CTPOW @ 0 DO CTARRAY I 2* + @
               TINT @ FLOAT I FLOAT F* SFREQ FLOAT F/
               XEND @ 2/ FLOAT F-
               CTSLOPE F@ F* INTEGER -
               CTAVER @ -
               CTARRAY I 2* + ! LOOP    % build new CTARRAY
;


"LOADING INTRR" MSG CR

:INTRR :                        % take the original array of RR and
                                % compute equally time spaced RR

  CTARRAY CTPTR !               % initialize pointer to array
  0 RREM !
  0 CURR !
  0 CTCOUNT !
                                % divide current RR (+ remainder
                                % of previous division) by TINT @ to
                                % know how many RR points to store of
                                % current RR value
```

```
  RRCOUNT @ 5 - 0 DO FOO I 2 * + @ DUP CURR !
           RREM @ + TINT @ U/MOD RREM !                % store remainder
                                                       % quotient is at top-1
          DUP QUOT !                                   % store as many current RR
                                                       % as indicated by QUOT
               0 DO CURR @ 1000 SFREQ U*/
                                          % convert RR to msec
               CTPUT CTCOUNT @ 1 + DUP CTCOUNT !       % Keep a counter to RR
               CTLEN 2 / UGE IF EXIT THEN
               LOOP
  CTCOUNT @ CTLEN 2 / UGE IF EXIT THEN
  LOOP

;

"LOADING CTPRE" MSG CR


:CTPRE :
  INTRR                % interpolate to obtain equally spaced RR int

                                                       % compute the highest power of
                                                       % 2 fitting in CTCOUNT
  SPSIZE                                               % this will be the array length
                                                       % for FFT

                                                       % compute max value for x-axis
  TINT @ CTPOW @ SFREQ  U*/ XEND !

  AVCT                                                 % compute average RR from
                                                       % equal time spaced array

  RRFIT                                                % fit straight line to CTARRAY

                                                       % subtract fitted line
  NEWCT                                    % subtract average

                                                       % compute min and max value
                                                       % of new CTARRAY
  CTARRAY CTPOW @ ARMAX
  CTARRAY CTPOW @ ARMIN


                                                       % use those to compute max
                                                       % and min value for Y-axis
  MAXVAL @ MINVAL @ ABS MAX                            % max deflection from average
                                                       % (in CTARRAY average should=0
 100 / 1 + 100 * YEND !                                % compute the smallest multiple
                                                       % of 100.=64H that contains max
                                                       % this max deflection
                                                       % and store in YEND
CTPOW @ 0 DO CTARRAY I 2* + @
       FLOAT FOO I 8 * + F!
       0.0 FOO I 8 * 4 + + F!
LOOP                                                   % has converted array to float
                                                       % and stored in real part of FOO
                                                       % 0.0 stored in imag.part of FOO
;

"LOADING RRPR" MSG CR

% procedure to scan,interpolate,DC trend fit the RR-array
% ------------------------------------------------------
% after loading all preiminary STOIC programs
```

```
% and opening the file
% say RSCAN



"LOADING IGRPLOT" MSG CR

'IGRPLOT :                          % plots an integer array where maxval is max y
                                    % should have length at top,address at top-1

  ARLEN ! ARADR !
  XLEFT @ ARADR @ @ YSPAN @ MAXVAL @ */ YLOW @ + MOVE
  ARLEN @ 0 DO I XSPAN @ ARLEN @ */ XLEFT @ +
               ARADR @ I 2* + @ YSPAN @ MAXVAL @ */ YLOW @ +
               DRAW LOOP
;

"LOADING RRGRF" MSG CR

'RRGRF :                            % plot RR array (equal tint ,-average,-line
                                    % fitted), with necessary offset on y-axis
                                    % should have array address at top-1
                                           %                "    length at top

  ARLEN ! ARADR !
  0 ARADR @ @ YEND @ + YSPAN @ YEND @ 2* */ MOVE
  ARLEN @ 0 DO I XSPAN @ ARLEN @ */
               ARADR @ I 2* + @ YEND @ + YSPAN @ YEND @ 2* */
               DRAW LOOP
;


"LOADING RRPLOT" MSG CR

'RRPLOT :
 CTPRE                  % main program that does all the fitting
                        % interpolation of data and preparation for plot
                        % and FFT
  DECIMAL
  PBOX
  () <#> XNFMT !                    % axis numberd as integers
  10 XTICKS
  0 XEND @ 10 / 10 XNUMBER
  "TIME (SEC)" XLABEL
  4 YTICKS
  YEND @ MINUS YEND @ 2 / 4 YNUMBER
  "RR-INTERVALS (MSEC)" YLABEL
  CTARRAY CTPOW @ RRGRF
PLTITL
;



RADIX !
;F
```

```
% FILE : HRSP
%       ROUTINES FOR STORING RR INTERVALS OUT OF TWAVE DISK DATA
%       INTO AN ARRAY OF INSTANTANEOUS AND LOW-PASS FILTERED HR
%       AND ANALYZING THIS ARRAY

% USE : bootstrap %PLOT
%       load        'GRAPH LOAD
%                   'HRSP LOAD
%                   'FOO IFILE OPEN
%                   DECIMAL
%                   PLOTTER
%       command  RSCAN
%                       RRCORR
%                   SPM1HZ
%                   'RRFFT LOAD
%                   HRFFT
%                   HRPLOT


RADIX @ DECIMAL

90 'TINT VARIABLE               % TIME INTERVAL BETWEEN INTERPOLATED RR-INT
0 'BPOS VARIABLE                % DISK POSITION (FIRST BYTE OF BLOCK)
0 'NBYTES VARIABLE              % NUMBER OF BYTES IN BLOCK
0 'PUTPTR VARIABLE              % POINTER TO ADDRESS IN RRARRAY
0 'RRCOUNT VARIABLE             % COUNTER TO CARDIAC BLOCKS ON FILE

0 'RRHIGH VARIABLE              % HIGH CUTOFF FOR DECIDING IF BAD POINT
0 'RRLOW VARIABLE               % LOW    "     "      "     "   "   "
0 'RRAVER VARIABLE              % AVERAGE RR-INTERVAL
                                % OF RRVALUES AT EQUAL TIME INTERVALS
0 'CTCOUNT VARIABLE             % COUNTER TO # INTERPOL.AND FILTERED HR POINTS
                                % IN FOO ARRAY (USUALLY 1024 UNLESS SHORT TRACE)
0 'CT2LN VARIABLE               % LOG2 ARRAY LENGTH FOR FFT
0 'CTPOW VARIABLE               % ARRAY LENGTH FOR FFT

0.0 'HRAVER FVARIABLE           % AVERAGE HR FROM FILTERED & INTERPOLATED ARRAY
0 'CTAVER VARIABLE              % USED ONLY IN RRFFT,DEFINED HERE TO ALLOW
0.0 'SMAVER FVARIABLE           % AVERAGE SAMPLE VALUE, "     "    "   "
0 'SMCHAN VARIABLE          % CHANNEL NUMBER FOR SMMSP
0.0 'RESPSIG FVARIABLE          % ST DEVIATION  FOR RESP
                                % DOUBLE PURPOSE OF RRFFT FOR RR-INT AND HR
0.0 'TTAVER FVARIABLE           % AVER TT PARAM,FOR MULTPLE USE OF RRFFT

0 'TPARAM VARIABLE              % INDEX FOR T-WAVE PARAM TO BE ANALYZED," " "
0 'PACEF VARIABLE               % PACING FREQ ,FOR MULTPLE USE OF RRFFT


0.0 'HRMIN FVARIABLE            % MINIMUM  "   "     "           "       "
0.0 'HRMAX FVARIABLE            % MAXIMUM  "   "     "           "       "

0 'ARADR VARIABLE               % ADDRESS FOR ARRAY TO BE PLOTTED
0 'ARLEN VARIABLE               % LENGTH   "   "     " "     "
0 'XEND VARIABLE                % HIGHER LIMIT FOR X-AXIS ON PLOT
0 'YEND VARIABLE                %    "     "    " Y  "    " "
0 'MAXVAL VARIABLE              % MAX VALUE OF VARIABLE ARRAY
0 'MINVAL VARIABLE              % MIN   "   "     "     "

0 'RRPTR VARIABLE               % ADDRESS FOR RR-VALUE TO BE CORRECTED
0 'NEWVAL VARIABLE              % NEW VALUE "     "     "   "   "

0.0 'FMAXVAL FVARIABLE          % MAX VALUE OF FLOATING PT ARRAY
0.0 'FREQMAX FVARIABLE          % MAX FREQUENCY IN SPECTRUM
```

```
0 'KMCOUNT VARIABLE             % COUNTER FOR RR-INTERVAL IMMEDIATELY
                                % FOLLOWING THE PRESENT i*tint
0 'KMMIN VARIABLE               % COUNTER FOR RR-INT FOLLOWING (i-1)*tint
0 'KMPLUS VARIABLE              %  "      "    "        "     (i+1)*tint

0.0 'AAHR FVARIABLE             % CORRECTION TO INSTANTANEOUS HR CORRESPONDING
                                % TO PRESENT i*tint
                                % AAHR=(MOLDTIME-(i-1)tint)/RRkmmin
0.0 'BBHR FVARIABLE             % CORRECTION TO HR
                                % BBHR=(NTIME-(i+1)tint)/RRkmplus

4 'MTIME ARRAY                  % TOTAL TIME ELAPSED FROM BEGINNING OF RRARRAY
                                % AT THE RR-INT FOLLOWING i*tint
4 'NTIME ARRAY                  % TOTAL TIME AT RR-INT FOLLOWING (i+1)*tint
4 'MOLDTIME ARRAY               %  "     "   "    "        "     (i-1)*tint
4 'ITINT ARRAY                  % i*tint
4 'DFITINT ARRAY                % USED FOR DOUBLE PRECISION SUBTRACTIONS


360 'SFREQ CONSTANT             % SAMPLING RATE 360.=168H

8192 'FOOLEN CONSTANT           % ARRAY LENGTH FOO   (1024.*8)
2536 'CTLEN CONSTANT            %   "     "  CTARRAY(1024.*2)
FOOLEN 'FOO ARRAY               % ARRAY FOR FLOAT REAL AND IM RR VALUES
                                % WILL STORE ORIGINAL RRARRAY TOO
                                % WILL STORE POWER SPECTRUM IN 1024 *4
CTLEN 'CTARRAY ARRAY            % "      "  INTERPOLATED RR VALUES

4000 'NCBLK CONSTANT            % # BLOCKS TO READ THROUGH TO HAVE ENOUGH
                                % CARDIAC BLOCKS



'GETWORD : GETBYTE GETBYTE 256 * + ;

'GET# : RDLINE WORD DROP . ILITERAL
        EQZ IF "INVALID NUMBER" ERR THEN ;

'FMAX : DOVER DOVER FLE IF DSWAP THEN 2DROP ;
'FMIN : DOVER DOVER FGE IF DSWAP THEN 2DROP ;

'RREOF :                        % when EOF block is met stop file scan
"RRCOUNT=" MSG
  RRCOUNT @ U=
  CR " EOF BLOCK ENCOUNTERED "MSG
;


'PUTRR :                        % stores RR and resets pointer to array
  PUTPTR @ ! PUTPTR @ 2 + PUTPTR !
;


'RRQRS :                        % read QRS block ,no need for obs time and no
                                % need for beat classification
  GETWORD GETWORD GETWORD 3DROP
  CR "RR  " MSG
                                % get and put the RR from 5th on

  RRCOUNT @ 1 + RRCOUNT !
RRCOUNT @ 5 GE IF GETWORD DUP PUTRR U= THEN
```

```
;

'DDQRS :                          % routine for finding the cardiac blocks
  GPOS DROP BPOS !                % get position and store
  GETWORD                         % get the type word
  GETWORD NBYTES !                % get # bytes and store
  DUP 3 EQ IF RRQRS THEN          % check if QRS block (type=3)
  DUP 5 EQ IF RREOF THEN          % check if EOF  "    ( "  =5)
  DROP
  BPOS @ NBYTES @ + 0 SPOS        % if none of both set the pos at next block
;


'RSCAN :                          % main program to read and store RR
  1024 0 SPOS
  0 RRCOUNT !
  FOO PUTPTR !
  NCBLK 0 DO RRCOUNT @ 5 - CTLEN 2/ LT IF DDQRS          % no need for more than
                                                         % about 1250 RRint
                                       ELSE CR "RRCOUNT>1200,EXIT" MSG EXIT
                                       THEN LOOP
;

'RRCORR :
0 0
  RRCOUNT @ 5 - 0 DO FOO I 2 * + @ M+ LOOP
  RRCOUNT @ 5 - UM/ DUP RRAVER ! CR "RRAVER=" MSG U= CR

  RRAVER @ FLOAT 1.6 F* INTEGER RRHIGH !
  RRAVER @ FLOAT .6 F* INTEGER RRLOW !
CR "POSSIBLE BAD POINTS" MSG
  RRCOUNT @ 5 - 0  DO FOO I 2* + @ DUP
                RRHIGH @ GE IF DUP CR = "AT I =" MSG I =
                               "   PRE: " MSG FOO I 1- 2* + @ =
                               "   AFT: " MSG FOO I 1+ 2* + @ =

           THEN DUP RRLOW @ LE IF DUP CR = "AT I=" MSG I =
                               "   PRE: " MSG FOO I 1- 2* + @ =
                               "   AFT: " MSG FOO I 1+ 2* + @ =
           THEN DROP LOOP
CR "ENTER CORRECTIONS IN FOO ARRAY OF RR-INTERVALS" MSG CR

25 0 DO "FIXPOINT?  " MSG
        GET#  DUP GTZ IF RRADR !
                                 " ? " MSG GET# FOO RRADR @ 2* + !
                      ELSE EXIT THEN
        LOOP

20 0 DO "INSERT?  " MSG
        GET# DUP GTZ IF RRADR !
                                  " ? " MSG GET# RRVAL !
                                 RRCOUNT @ 5 - RRADR @ DO FOO I' 2* + @
                                                       FOO I' 1+ 2* + !
                                               LOOP
              % RRvalues from RRADR on,moved up by 1 address
              % new value will be inserted at FOO+RRADR
              % RRCOUNT to be incremented
                                 RRVAL @ FOO RRADR @ 2* + !
                                 RRCOUNT @ 1+ RRCOUNT !
                      ELSE EXIT THEN
        LOOP
```

```
20 0 DO "DELETE?  " MSG
        GET# DUP GTZ IF RRADR !
                                RRCOUNT @ 5 - 1- RRADR @ DO FOO I 1+ 2* + @
                                                    FOO I 2* + !
                                                LOOP
                % RRvalues from RRADR on ,moved back by 1 address
                % RRCOUNT to be decremented
                                        RRCOUNT @ 1- RRCOUNT !
                        ELSE EXIT THEN
        LOOP

CR " RR-ARRAY CORRECTED" MSG CR


;

% now the original RRarray is built up (in FOO)
% an equal time interval array CTARRAY will be computed
% the DC drift subtracted keeping the average RR constant
% and the average RR will be subtracted too



'ARMAX :                        % has to be provided with array adress at top-1
                                %                                "   length at top
  SWAP
  DUP ARADR ! @          % copy address and get first value
  SWAP 1 DO ARADR @ I 2* + @ MAX LOOP MAXVAL !
;

'ARMIN :                        % has to be provided with array address at top-1
                                %                                "   length at top
  SWAP
  DUP ARADR ! @
  SWAP 1 DO ARADR @ I 2* + @ MIN LOOP MINVAL !
;



"LOADING CTMOVE" MSG CR
'CTMOVE :
  RRCOUNT @ 5 - CTLEN 2/ MIN
          0 DO FOO I 2* + @
                CTARRAY I 2* + !
                LOOP
;


% the original rrarray is now in CTarray
% will be filtered and interpolated simultaneouly using a rectangular
% window of width 2*tint


"LOADING DUBGET" MSG CR
'DUBGET :                       % puts at top-2 the lowest word
                                %      at top ,the highest word of
                                % dubbel precision integer
                        % requires pointer to lower word on top of stack
  DUP 2+ SWAP @ SWAP @
```

```
;

'DUBPUT :                % requires on stack lower word,higher word and pointer
  DUP 2SWAP              % has now low,pointer,high,pointer on stack
  2+ ! !
;

"LOADING INCITINT" MSG CR

'INCITINT :              % increment i*tint to (i+1)*tint and store new value
  ITINT DUBGET TINT @ M+
  ITINT DUBPUT
;

"LOADING INCNTIME" MSG CR
'INCNTIME :              % increments KMPLUS
                         % adds to NTIME the next RR-int,being RRkmplus
  KMPLUS 1+!
  NTIME DUBGET
  CTARRAY KMPLUS @ 2* + @ M+ NTIME DUBPUT
;

"LOADING SD@-" MSG CR

'SD@- CODE<
        D POP, H POP,
        D LDAX, M SUB, A M MOV, H INX, D INX,
        D LDAX, M SBB, A M MOV, H INX, D INX,
        D LDAX, M SBB, A M MOV, H INX, D INX,
        D LDAX, M SBB, A M MOV,
        0PUSH JP,
        -1PUSH JM, >

 "LOADING HRPRE" MSG CR


'HRPRE :
CR "RRAVER (IN CLOCK COUNTS)=" MSG RRAVER @ = CR

  CTMOVE                 % moves the original RRint from FOOarray to CTarray


  0 0 MOLDTIME DUBPUT
  0 0 MTIME DUBPUT
  0 0 NTIME DUBPUT
  0 0 ITINT DUBPUT
  0 0 DFITINT DUBPUT

  0 KMCOUNT ! 0 KMPLUS ! 0 KMMIN !

% initialize all variables
% first find first NTIME and KMPLUS values before loop is started

10 0 DO INCNTIME               % increment NTIME
        NTIME @                % is still small,thus no double integer
        TINT @ - GTZ IF NTIME @ "FIRST NTIME= " MSG = CR EXIT
        THEN LOOP

% the NTIME value is stored in NTIME
% while the old MTIME value becomes MOLDTIME
% when the do loop is started for computing the instantaneous filtered
% HR at absolute times i*tint
```

```
1025 1 DO INCITINT              % increment previous i*tint
       KMCOUNT @ KMMIN ! MTIME DUBGET MOLDTIME DUBPUT
       KMPLUS @ KMCOUNT ! NTIME DUBGET MTIME DUBPUT
                                % has defined new MOLDTIME and MTIME
                                % search for new NTIME
   10 0 DO
                                        % check if NTIME and KMPLUS
                                        % larger than (i+1)*tint
       ITINT DUBGET TINT @ M+ DFITINT DUBPUT
       DFITINT NTIME SD@-               % compute (i+1)*tint-NTIME
                                        % returns sign on stack
                                        % and difference in DFITINT,if neg
       LTZ IF INCNTIME                  % increment NTIME and KMPLUS
             ELSE EXIT THEN
     LOOP

DFITINT 2+ @ LTZ IF CR "AFTER 10 STEPS STILL NTIME < (I+1)*TINT" MSG CR THEN
                                        % this can happen at end of RRarray or
                                        % if something wrong

% KMMIN @ "KMMIN=" MSG =
% KMPLUS @ "KMPLUS=" MSG =
RRCOUNT @ 5 - CTLEN 2/ MIN KMPLUS @ GE IF



                                % now new NTIME and KMPLUS is found


             % compute now BBHR= ((i+1)*tint-(NTIME-RRKmplus))/RRKmplus

             %     or          = (RRKmplus,DFITINT)/RRKmplus

   DFITINT @ FLOAT                      % this difference is a single prec.int
               -1. F*
    CTARRAY KMPLUS @ 2* + @ FLOAT F+    %  on stack now (RRKmplus-DFTINT)
    CTARRAY KMPLUS @ 2* + @ FLOAT F/ DDUP FLTZ IF "BBHR NEG,ERROR" MSG THEN
    BBHR F!



                                % compute AAHR= (MOLDTIME-(i-1)*tint)/RRKmmin
  ITINT DUBGET TINT @ M- DFITINT DUBPUT
  DFITINT MOLDTIME SD@-
     GTZ IF "MOLDTIME IS NOT LARGER THAN (I-1)*TINT,ERROR" ERR
     THEN
  DFITINT @ FLOAT               % the diff will only be single precision integer
  CTARRAY KMMIN @ 2* + @ FLOAT F/ AAHR F!



                                % compute the HR value to be stored in the
                                % FOO array as floating point in the real part
             % HRi= (AAHR+BBHR+KMPLUS-KMMIN+1)/(2*TINT)
   AAHR F@ BBHR F@ F+
  KMPLUS @ KMMIN @ - 1 - FLOAT F+
  TINT @ 2* FLOAT F/ SFREQ FLOAT F*             % gives HRi in units of 1/sec

%  DDUP "  HR(I)= " MSG F= "  I= " MSG I = CR
 DDUP
                                        FLTZ IF "HR(I) NEG" ERR THEN

FOO I 1- 8 * + F!
```

```
0.0 FOO I 1- 8 * 4 + + F!

) I CTCOUNT ! ELSE EXIT THEN
  LOOP
  ;




  % ------------------------


  'AVHR : 0.0 HRAVER F!
    CTPOW @ 0 DO FOO I 8 * + F@
                HRAVER F@ F+ HRAVER F! LOOP
    HRAVER F@ CTPOW @ FLOAT F/ DDUP "HRAVER=" MSG F= HRAVER F!
  ;

  'MAXHR : FOO F@
  CTPOW @ 1 DO FOO I 8 * + F@ FMAX LOOP
    DDUP HRMAX F! CR "HRMAX=" MSG F=
  ;

  'MINHR : FOO F@
  CTPOW @ 1 DO FOO I 8 * + F@ FMIN LOOP
    DDUP HRMIN F! CR "HRMIN=" MSG F=
  ;
  "LOADING SPSIZE" MSG

  'SPSIZE :
    CTCOUNT @ FLOAT FLOG2 INTEGER CT2LN !
  1 CT2LN @ 0 DO 2* LOOP CTPOW !
  CR " # POINTS TO BE USED FOR FFT IS " MSG CTPOW @ U= CR
  ;


  "LOADING CTPRE" MSG


  'CTPRE :
    HRPRE                  % filter and interpolate to obtain equally spaced HR
                           % array placed already in real elements of FOO array

                                          % compute the highest power of
                                          % 2 fitting in CTCOUNT
    SPSIZE                                % this will be the array length
                                          % for FFT
                                          % usually 1024

                                          % compute max value for x-axis
    TINT @ CTPOW @ SFREQ  U*/ XEND !

    0.1                                   % compute average HR from
                                          % equal time spaced array

    MAXHR MINHR                     % compute min and max value
                                          % of new HRarray
```

```
;

% procedure to scan,filter & interpolate,the RR-array to HR-array
% ------------------------------------------------------------
% after loading all preiminary STOIC programs
% and opening the file
% say RSCAN



'HRSCALE :                          % has HRvalue on stack,will scale to
                                    % (HR(i)-HRMIN)*YSPAN/(hrmax-hrmin)
  HRMIN F@ F-
  YSPAN @ FLOAT F*
  HRMAX F@ HRMIN F@ F- F/ INTEGER YLOW @ +
;

'HRGRF :
XLEFT @ FOO F@ HRSCALE MOVE
CTPOW @ 1 DO I XSPAN @ CTPOW @ */ XLEFT @ +
          FOO I 8 * + F@ HRSCALE DRAW LOOP 1000 800 MOVE
;


"LOADING HRPLOT" MSG CR

'HRPLOT :
CTPRE           % main program that does the filtering+intepolating
                % of the data and preparation of the data for plot
                % and FFT
  DECIMAL
  PBOX
  () <#> XNFMT !                        % axis numberd as integers
  10 XTICKS
  0 XEND @ 10 / 10 XNUMBER
  "TIME (SEC)" XLABEL

  4 YTICKS
       HRMIN F@ 60 FLOAT F* INTEGER                    % y-origin
     HRMAX F@ HRMIN F@ F- 60 FLOAT F* 4. F/ INTEGER    % gives delta-y
       4                                    % number of delta-y
       YNUMBER

  "INSTANTANEOUS HR  (B/MIN)" YLABEL
  HRGRF
PLTITL
;



RADIX !
;F
```

```
% FILE : SMMSP

% USE : bootstrap %PLOT
%       load        'GPAPH LOAD
%                   'SMMSP LOAD
%                   'FOO IFILE OPEN
%                   DECIMAL
%                   PLOTTER
%       command  SMSCAN
%                   SMPLOT
%                   'RRFFT LOAD
%                   SMFFT
%                   SPM1HZ


RADIX @ DECIMAL

90 'TINT VARIABLE                % TIME INTERVAL BETWEEN INTERPOLATED RR-INT
0 'BPOS VARIABLE                 % DISK POSITION (FIRST BYTE OF BLOCK)
0 'NBYTES VARIABLE               % NUMBER OF BYTES IN BLOCK
0 'PUTPTR VARIABLE               % POINTER TO ADDRESS IN RRARRAY
0 'RRCOUNT VARIABLE              % COUNTER TO CARDIAC BLOCKS ON FILE

0.0 'HRAVER FVARIABLE            % AVERAGE HR FROM FILTERED & INTERPOLATED ARRAY
                                 % DEFINED TO ALLOW TRIPLE PURPOSE USE OF RRFFT
0 'CTAVER VARIABLE               % USED ONLY IN RRFFT,DEFINED HERE TO ALLOW
                                 % DOUBLE PURPOSE OF RRFFT FOR RR-INT AND HR
0.0 'TTAVER FVARIABLE            % AVER TWAVE PARAM,FOR RRFFT MULTIPLE USE
0 'TPARAM VARIABLE               % INDEX FOR "  " TO BE ANALYZED, " " " "
0 'PACEF VARIABLE                % PACING FREQ DEFINED FOR RRFFT "     "

0 'XEND VARIABLE                 % HIGHER LIMIT FOR X-AXIS ON PLOT

0.0 'FMAXVAL FVARIABLE           % MAX VALUE OF FLOATING PT ARRAY
0.0 'FREQMAX FVARIABLE           % MAX FREQUENCY IN SPECTRUM

0 'CTPOW VARIABLE                % LENGTH OF ARRAY TO BE USED FOR FFT
0 'CT2LN VARIABLE                % POWER OF 2 FITTING IN ARRAY LENGTH (LOG2)

0 'ARLEN VARIABLE                % GENERAL ARRAY LENGTH
0 'ARADR VARIABLE                %   "      "    ADDRESS,DEFINED FOR RRFFT

360 'SFREQ CONSTANT              % SAMPLING RATE 360.=168H

8192 'FOOLEN CONSTANT            % ARRAY LENGTH FOO   (1024.*8)
2536 'CTLEN CONSTANT             %   "     "  CTARRAY(1024.*2)
FOOLEN 'FOO ARRAY                % ARRAY FOR FLOAT REAL AND IM RR VALUES
                                 % WILL STORE ORIGINAL RRARRAY TOO
                                 % WILL STORE POWER SPECTRUM IN 1024 *4
CTLEN 'CTARRAY ARRAY             % "      "  INTERPOLATED RR VALUES

4000 'NCBLK CONSTANT             % # BLOCKS TO READ THROUGH TO HAVE ENOUGH
                                 % CARDIAC BLOCKS


% previous variables and arrays are common to HRSP and SMMSP
% following ones only for SMMSP

2 'SMPL 1 CONSTANT               % # SAMPLES TO TAKE [illegible] EVERY SECOND
                                 % SAMPLE ,SINCE ORIGINAL SAMPLING RATE
                                 % WAS TWICE THE SAMPLING RATE FOR HEARTRATE
0 'SMCHAN VARIABLE               % WHICH CHANNEL NUMBER TO ANALYZE
0 'NCHAN VARIABLE                % # CHANNELS
```

```
0 'NSUBBL VARIABLE              % # SUBBLOCKS
0 'SMCOUNT VARIABLE             % # SAMPLES PUT IN ARRAY
0.0 'SMAVER FVARIABLE           % AVERAGE SAMPLE VALUE
0.0 'SMMIN FVARIABLE            % MIN SAMPLE VALUE
0.0 'SMMAX FVARIABLE            % MAX  "       "
0.0 'RESPSIG FVARIABLE          % STANDARD DEVIATION OF RESPIRATION SIGNAL
                                % USED TO NORMALIZE THE  " SPECTRUM


'GETWORD : GETBYTE GETBYTE 256 * + ;

'GET# : RDLINE WORD DROP . ILITERAL
     EQZ IF "INVALID NUMBER" ERR THEN ;

'FMAX : DOVER DOVER FLE IF DSWAP THEN 2DROP ;

'FMIN : DOVER DOVER FGE IF DSWAP THEN 2DROP ;

'RREOF :                        % when EOF block is met stop file scan
CR "RRCOUNT =" MSG
  RRCOUNT @ U=
  CR " EOF BLOCK ENCOUNTERED " MSG
;


'PUTSM :                        % stores SM and resets poanter to array
DUP = CR FLOAT
  PUTPTR @ F! PUTPTR @ 4 + PUTPTR !
;


'SAMPSM :                       % read the sample values from chosen channel
                                % and puts then in array(FOO)
  GETWORD NCHAN !               % # channels in this run
  GETWORD GETWORD 2DROP                 % no need for absolute time
  NBYTES @ 10 - 2/              % (# bytes in block -# header bytes)/(2*nchan)
       NCHAN @ / NSUBBL !               %  is # subblocks
                                        % each subblock contains 1 sample from
                                        % each channel
 NSUBBL @ 0 DO SMCHAN @ 1- 0 DO GETWORD DROP LOOP
               GETWORD PUTSM SMCOUNT 1+!
               NCHAN @ SMCHAN @ - 0 DO GETWORD DROP LOOP
          SMCOUNT @ SMNUM GE IF EXIT THEN
        LOOP
                                % in each subblock the samples from the unwanted
                                % channels are dropped,the wanted are stored
                                % tot # samples from wanted channel should
                                % not exceed 2048 ,each second sample will be
                                % discarded
;

'DDSAMP :                       % routine for finding the sample blocks
  GPOS DROP BPOS !              % get position and store
  GETWORD                       % get the type word
  GETWORD NBYTES !              % get # bytes and store
  DUP 3 EQ IF RRCOUNT 1+! THEN  % check if QRS block (type=3)
RRCOUNT @ 5 GE IF DUP 2 EQ IF SAMPSM THEN THEN
                        % only after fifth QRS check if a sample block(=2)
  DUP 5 EQ IF RREOF THEN        % check if EOF  "     ( "  =5)
  DROP
  BPOS @ NBYTES @ + 0 SPOS      % if none of both set the pos at next block
;
```

```
'SMSCAN :                       % main program to read and store samples
  SMCHAN !                      % has to be CALLED with specification of
                                % CHANNEL NUMBER
                                % "1 SMSCAN" or "2 SMSCAN" etc...
  1024 0 SPOS
  0 SMCOUNT ! 0 RRCOUNT !
  FOO PUTPTR !
  NCBLK 0 DO SMCOUNT @ SMNUM LT IF DDSAMP ELSE EXIT THEN LOOP
;



% now the original SMarray is built up (in FOO)
% is already floating point
% every second sample (meanwhile stored in the imaginary addresses of FOO)
% will be deleted


% ------------------------


'AVSM : 0.0 SMAVER F!
  CTPOW @ 0 DO FOO I 8 * + F@
               SMAVER F@ F+ SMAVER F! LOOP
  SMAVER F@ CTPOW @ FLOAT F/ DDUP "SMAVER=" MSG F= SMAVER F!
;

'MAXSM : FOO F@
CTPOW @ 1 DO FOO I 8 * + F@ FMAX LOOP
  DDUP SMMAX F! CR "SMMAX=" MSG F=
;

'MINSM : FOO F@
CTPOW @ 1 DO FOO I 8 * + F@ FMIN LOOP
  DDUP SMMIN F! CR "SMMIN=" MSG F=
;


CR "LOADING SMSIG" MSG CR

'SMSIG : 0.0 RESPSIG F!
        CTPOW @ 0 DO FOO I 8 * + F@
                     SMAVER F@ F- DDUP F*
                    RESPSIG F@ F+ RESPSIG F! LOOP
        RESPSIG F@ CTPOW @ 1- FLOAT F/
        FSQRT RESPSIG F!
;

"LOADING CTPRE" MSG


'CTPRE :
 1024 0 DO
           0.0 FOO I 8 * 4 + + F! LOOP % drop every second sample

               % normally SMNUM and SMNUM/2 should be a power of 2
  SMCOUNT @ 2/ FLOAT FLOG2 INTEGER CT2LN !              % power of 2 of array length
 1 CT2LN @ 0 DO 2* LOOP CTPOW !         % compute length to fill in array
  CTPOW @ "CTPOW=" MSG =                        % necessary for FFT

                                                % compute max value for x-axis
  TINT @ CTPOW @ SFREQ  U*/ XEND !
```

```
  AVSM                                    % compute average SM from
                                          % equal time spaced array

  MAXSM MINSM                             % compute min and max value
                                          % of  SMarray

SMCHAN @ 2 EQ IF SMSIG          % compute standard deviation from
                                % mean for resp signal
CR "RESPIRATION RANGE =RESPSIG = " MSG RESPSIG F@ F= THEN
;


% procedure to scan samples and store in FOO array,ready for FFT
% -------------------------------------------------------------
% after loading all preiminary STOIC programs
% and opening the file
% say SMSCAN



'SMSCALE :                      % has SMvalue on stack,will scale to
                                % (SM(i)-SMMIN)*YSPAN/(smmax-smmin)
  SMMIN F@ F-
  YSPAN @ FLOAT F*
  SMMAX F@ SMMIN F@ F- F/ INTEGER YLOW @ +
;

'SMGRF :
XLEFT @ FOO F@ SMSCALE MOVE
CTPOW @ 1 DO I XSPAN @ CTPOW @ */ XLEFT @ +
          FOO I 8 * + F@ SMSCALE DRAW LOOP 1000 800 MOVE
;


"LOADING SMPLOT" MSG CR

'SMPLOT :
CTPRE                   % main program prepares samples for plot
                        % and FFT
  DECIMAL
  PBOX
  () <#> XNFMT !                        % axis numberd as integers
  10 XTICKS
  0 XEND @ 10 / 10 XNUMBER
  "TIME (SEC)" XLABEL

  4 YTICKS
       SMMIN F@ INTEGER                         % y-origin
      SMMAX F@ SMMIN F@ F- 4. F/ INTEGER        % gives delta-y
        4                                       % number of delta-y
        YNUMBER

  "SAMPLE VALUES" YLABEL
SMGRF
;


RADIX !
```

```
% FILE : RRFFT
%          COMPUTES FFT OF RRINTERVALS AND PLOTS THE SPECTRUM

RADIX @ DECIMAL

0    'HRHRHR VARIABLE            % flag  =0 if RRint analyzed
                                 %       =1 if HR      "

3    'PSPAN VARIABLE             % span (and # ticks) on Y-axis
                                 % in 0.01 "power units"
1    'PSDIV VARIABLE             % result of PSPAN/10,used for Y-axis
0.01 'FREDEL FVARIABLE           % delta frequency in spectrum

1.0  'YSPMAX FVARIABLE           % span for plot on y-axis

0.0 'F1INT FVARIABLE             % integral over part of spectrum
0 'LOWLIM VARIABLE               % serial # of spectral value corresponding
                                 % to low lim of integral
0 'HILIM VARIABLE                % same for high freq lim of int

0.0 'SPAVER FVARIABLE            % will contain the average of the variable to
                                 % be analyzed by RRFFT


.001 'F10MUL FVARIABLE  % determines decimal range for Y plot
3    'DECRANGE VARIABLE          %   "       # digits after decimall point


'FGET# : RDLINE WORD DROP . FLITERAL EQZ IF
         "INVALID FLOATING POINT NUMBER" ERR THEN ;

"FILTCORR LOAD" MSG
'FILTCORR :
                                 % corrects for filter attenuation in region
                                 % up to 2 hz
  CTPOW @ 2/ 1 DO I FLOAT 512 FLOAT F/ 3.141593 F* 2. F/ DDUP
              FSIN F/
                                 % computes x/sinx when x=(i* 3.14/2)/512
              DDUP
              FOO I 8 * + F@ F* FOO I 8 * + F!
       DDUP FOO CTPOW @ I - 8 * + F@ F* FOO CTPOW @ I - 8 * + F!
       DDUP FOO I 8 * + 4 + F@ F*  FOO I 8 * + 4 + F!
            FOO CTPOW @ I - 8 * + 4 + F@ F* FOO CTPOW @ I - 8 * + 4 + F!
              LOOP
CR "FILTER ATTENUATION CORRECTED" MSG CR
;

"FFTFF LOAD" MSG


'FFTFF :                         % computes FFT of array FOOarray

  FOO CT2LN @  FFT                              % COMPUTE FFT

"FFT DONE" MSG
HRHRHR @ 1 EQ IF FILTCORR THEN          % correct for unwanted filter
                                        % attenuation at low frequencies
                                        % when filtered HR is analyzed
                                        % COMPUTE POWER SPECTRUM
  CTPOW @   0 DO FOO I 8 * + F@ DDUP F*
            FOO I 8 * 4 + + F@ DDUP F* F+
                                TINT @ FLOAT SFREQ FLOAT F/ F*
                                SPAVER F@ DDUP F* F/
```

```
                        % square real,square imag,add squares,
                        % multiply by TINT/SFREQ
                        % normalize by CTAVER↑2 to obtain normalized
                        % power spectrum of RRfluct
                        % or by HRAVER↑2 for HRspectrum normalization
                        % or by SMaver↑2  "  SM   "          "

%          DDUP F= CR
           FOO  I 4 * +  F!            % store power sp in FOO
  LOOP

  0.0 FOO F!            % first point zeroed  (temporarily)   !!!!!!!!!!!!


                        % compute max frequency and delta frequency for
                        % RRFFT, HRFFT ,SMFFT but not for TTFFT

HRHRHR @ 3 NE IF
       SFREQ FLOAT TINT @ FLOAT F/ CTPOW @ FLOAT F/ FREDEL F!
                                    % computation of delta frequency
     SFREQ FLOAT TINT @ 2* FLOAT F/ FREQMAX F!
                                    % computation of max freq in spectrum
  THEN
;


CR "SUBAVER LOAD" MSG CR

'SUBAVER :                          % subtract average before computing FFT
         CTPOW @ 0 DO FOO I 8 * + F@ SPAVER F@ F-
                        FOO I 8 * + F! LOOP
;


"RRFFT LOAD" MSG

'RRFFT : 0 HRHRHR !
         CTAVER @ FLOAT SPAVER F!       % average value to be used for norm.
          FFTFF ;               % spectrum of RRint

'HRFFT : 1 HRHRHR !
         HRAVER F@ SPAVER F!
        SUBAVER                         % subtract average value
          FFTFF ;               %  "       "  HR

'SMFFT : 2 HRHRHR !
           SMAVER F@ SPAVER F!
                CR " SPAVER = " MSG SPAVER F@ F= CR
        SUBAVER                         % subtract average value
                "AVERAGE VALUE SUBTRACTED" MSG CR
        SMCHAN @ 2 EQ IF " RESPSIG STORED INTO SPAVER=" MSG
                RESPSIG F@ DDUP SPAVER F! F= THEN CR    % for respiration
                                                        % normalize by standard
                                                        % deviation**2
          FFTFF ;               % spectrum of sample channel

'TTFFT : 3 HRHRHR !
         PACEF @ FLOAT 60. F/ 2. F/ FREQMAX F!
         PACEF @ FLOAT 60. F/ CTPOW @ FLOAT F/ FREDEL F!
                                    % define max freq and delta freq for
        TTAVER F@ SPAVER F!
        SUBAVER                         % subtract average value
        "FOR TPARAM=1,2 OR 3 THE SPECTRUM IS NORMALIZED BY SPAVER**2" MSG CR
```

```
TPARAM @ 0 EQ IF "SPECTRUM NORMALIZED BY 1 ,NOT BY SPAVER**2" MSG CR
                 1.0 SPAVER F! THEN
```



```
                % for baseline fluct (TPARAM=0)
                % the spectrum is normalized by 1

    FFTFF ;     % spectrum of Twave param


"PEAKINT LOAD" MSG


'PEAKINT :                  % computes integral on peak in spectrum
                            % exspects high freq on top
                            %  "       low    "   "  top-1

0.0 F1INT F!
FREDEL F@ F/ .5 F+ INTEGER HILIM !
FREDEL F@ F/ .5 F+ INTEGER LOWLIM !

FOO LOWLIM @ 4 * + F@
FOO HILIM @ 4 * + F@ F+ 2. F/ F1INT F!
HILIM @ LOWLIM @ 1+ DO FOO I 4 * + F@
                 F1INT F@ F+ F1INT F! LOOP
F1INT F@ FREDEL F@ F* "INTEGRAL ON THIS AREA IS " MSG F=
;



"FARMAX LOAD" MSG

'FARMAX :                           %  computes floating pt max
                                    % has to be provided with
                                    %       array address at top-1
                                    %          "    length at top
0.0 FMAXVAL F!
  ARLEN !   DUP ARADR ! F@
  ARLEN @ 1 DO  ARADR @ I 4 * + F@ FMAX LOOP
  DDUP FMAXVAL F! "FMAXVAL =" MSG F=

;


'SPMAX : ARLEN !
       FOO 2 4 * + F@
  ARLEN @ 3 DO FOO I 4 * + F@ FMAX LOOP
       DDUP FMAXVAL F! "FMAXVAL= " MSG F=
;


CR "SPRANGE LOAD" MSG

'SPRANGE :
                            % determines range for Yscale of plots
              % initialize decimal range and # digits after dec point

              % if .1< data <1. then 2 decimals
              % if .01<data <.1   "  3   "
              % if .001<data<.01  "  4   "      etc...

.001 F10MUL F!    3 DECRANGE !
YSPMAX F@ BEGIN DDUP .1 FGE IF F10MUL F@ 10. F* F10MUL F!
```

```
                                DECRANGE 1-!
                                10. F/ REPEAT
          BEGIN DDUP .01 FLE IF F10MUL F@ 10. F/ F10MUL F!
                                 DECRANGE 1+!
                                 10. F* REPEAT
  2DROP
CR DECRANGE @ = "  IS STORED IN NDP" MSG CR

;


CR "XSPSCALE LOAD " MSG

'XSPSCALE :

                          % computes the corresponding frequency value
                          % checks if not larger than 1 hz
                          % and scales it to XSPAN
  FLOAT FREDEL F@ F* FREQMAX F@ F/ XSPAN @ FLOAT F* INTEGER XLEFT @ +
  ;

" YSPSCALE LOAD " MSG

'YSPSCALE :
                          % scales the spectral values so that YSPMAX
                          % corresponds to YSPAN
  YSPMAX F@ F/ YSPAN @ FLOAT F* INTEGER YLOW @ +
;


" SGRPLOT LOAD " MSG

'SGRPLOT :                                % plots spectrum
                                  % to be provided with array address (top-1)
                                  % and length (top)
  ARLEN ! ARADR
  0 XSPSCALE 0 YSPSCALE MOVE
  ARLEN @ 0 DO I XSPSCALE
               ARADR @ I 4 * + F@ YSPSCALE DRAW LOOP
;

"SMGRPLOT LOAD " MSG

'SMGRPLOT :                               % plots a smoothed spectrum
                            % .0382*(n-2)+.2618*(n-1)+.4*n+.2618*(n+1)+.0382*(n+2)
  ARLEN ! ARADR !
5 XSPSCALE
        ARADR @ 5 4 * + F@ .4 F*
        ARADR @ 5 4 * 4 - + F@
        ARADR @ 5 4 * 4 + + F@ F+ .2618 F* F+
        ARADR @ 5 4 * 8 - + F@
        ARADR @ 5 4 * 8 + + F@ F+ .0382 F* F+
  YSPSCALE MOVE                           % move to first point to be drawn


  ARLEN @ 5 DO I XSPSCALE
                ARADR @ I 4 * + F@ 0.4 F*
                ARADR @ I 4 * 4 - + F@
                ARADR @ I 4 * 4 + + F@ F+ 0.2618 F* F+
                ARADR @ I 4 * 8 - + F@
                ARADR @ I 4 * 8 + + F@ F+ 0.0382 F* F+
                  YSPSCALE DRAW LOOP
  ;
```

```
'SAVPLOT :                          % plots each spectral point as an average of 5
  ARLEN ! ARADR !
5 XSPSCALE
        ARADR @ 5 4 * + F@
        ARADR @ 4 4 * + F@
        ARADR @ 3 4 * + F@
        ARADR @ 6 4 * + F@
        ARADR @ 7 4 * + F@ F+ F+ F+ F+ 5. F/
YSPSCALE MOVE                               % move to first point to be drawn

ARLEN @ 5 DO I XSPSCALE
                ARADR @ I 4 * + F@
                ARADR @ I 4 * 4 - + F@
                ARADR @ I 4 * 4 + + F@
                ARADR @ I 4 * 8 - + F@
                ARADR @ I 4 * 8 + + F@ F+ F+ F+ F+ 5. F/
              YSPSCALE DRAW LOOP
;

"SPBOX LOADING" MSG


'SPBOX :
  DECIMAL
  ().DP<#> XNFMT !
  PBOX
  10 XTICKS
2 NDP ! 0 FREQMAX F@ 10 FLOAT F* INTEGER 10 XNUMBER
                        % freqmax/10 is the delta-x for x-axis but since it
                        % has to be *100 before 2 decimal points are taken
                        % freqmax*10 is used
  "FREQUENCY (HZ)" XLABEL

%   PSPAN @ 1- 10 / 1+ PSDIV !          % PSDIV will =1 when PSPAN<10
%                                       %  "      "  =2   "  10<PSPAN<20  etc...
%   PSPAN @ PSDIV @ / YTICKS            % # ticks =PSPAN for PSPAN<10
%                                       % # ticks =PSPAN/2 for 10<PSPAN<20 etc..
%   2 NDP ! 0 PSDIV @ PSPAN @ PSDIV @ / YNUMBER
%                                       % the number next to each tick will
%                                       % be a multiple of PSDIV*.01


4 YTICKS
DECRANGE @ NDP ! 0 YSPMAX F@ 4. F/ F10MUL F@ F/ INTEGER 4 YNUMBER

                                        % more general plot version
                                        % handling large ranges of data


  HRHRHR @ EQZ IF "RR-INTERVAL POWER SPECTRUM" YLABEL THEN
  HRHRHR @ 1 EQ IF "INSTANTANEOUS HEART-RATE FLUCTUATIONS SPECTRUM" YLABEL THEN
HRHRHR @ 2 EQ IF " SAMPLE CHANNEL SPECTRUM" YLABEL THEN
HRHRHR @ 3 EQ IF "T-WAVE PARAMETER FLUCTUATION SPECTRUM" YLABEL THEN

;

"RNDPSP LOAD " MSG


'RNDPSP :                           % round off PSPAN to multiple of 10 and add 1
                                    % if PSPAN is larger than 100
```

```
PSPAN @ 100 GE IF PSPAN @ 5 + 10 / 10 * PSPAN ! THEN ;


'SPSCALE :

   FREQMAX F@ FREDEL F@ F/ INTEGER 1+ SPMAX
                                        % max of array FOO is computed
                                        % arraylength is CTPOW/2+1 or
                                        % FREQMAX/FREDEL+1

  "  IS MAX SPECTRAL VALUE" MSG CR


%   "YSPMAX, THE MAX VALUE ON Y-AXIS, IS DEFINED AS  PSPAN*.01 " MSG CR
%   "PSPAN ? (INTEGER) " MSG
%   GET# PSPAN !
%         RNDPSP                        % rounds off PSPAN if > 100
%         PSPAN @ FLOAT .01 F* YSPMAX F!        % store max y

" ENTER YSPMAX , THE REAL FP MAXIMUM FOR Y SCALE" MSG
CR " YSPMAX ?" MSG FGET#
YSPMAX F!

SPRANGE
                                        % more general version handling
                                        % large ranges of data
;

'SPPLOT : SPSCALE
        SPBOX
        FOO FREQMAX F@ FREDEL F@ F/ INTEGER 1+ SGRPLOT
;


'SPSMO : SPSCALE
         SPBOX
         FOO FREQMAX F@ FREDEL F@ F/ INTEGER 1+ SMGRPLOT
;

'SP5AV : SPSCALE SPBOX
        FOO FREQMAX F@ FREDEL F@ F/ INTEGER 1+ 5AVPLOT
;


'SP1HZ : 1. FREQMAX F! SPSCALE
         SPBOX
         FOO FREQMAX F@ FREDEL F@ F/ INTEGER 1+ SGRPLOT
;

'SPM1HZ : 1. FREQMAX F!  SPSCALE
          SPBOX
          FOO FREQMAX F@ FREDEL F@ F/ INTEGER 1+ SMGRPLOT
;


'5AV1HZ : 1. FREQMAX F! SPSCALE
          SPBOX
          FOO FREQMAX F@ FREDEL F@ F/ INTEGER 1+ 5AVPLOT
;

RADIX !
:F
```