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Pulse Analysis as a Possible Real-Time Biomarker Complementary to SGPT and SGOT for Monitoring Acute Hepatotoxicity

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Based on the resonance theory, the pressure wave of the arterial system could reflect the physical condition of the internal organs. Experimental evidence indicates that the physical condition of organs is related to various Fourier components of the pressure pulse. We have proved that the first harmonic of the pressure-wave spectrum is closely related to the liver.

In this study, Wistar rats given massive doses of acetaminophen were examined. The amplitude of the first harmonic of the blood pressure pulse, A1, was analyzed and correlated with the blood liver function indexes that examine serum glutamate pyruvate transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT). When A1 was below 3650 and SGPT was above 90, the kappa value was about 0.6; the probability is greater than .999 based on a chi-square test. When A1 was below 3650 and SGOT was above 380, the kappa value was around 0.5; the probability is greater than .999.

Our results indicate that A1 may be used as a simple, real-time biomarker that is complementary to the commonly used first-line liver indicators, SGPT and SGOT levels, for monitoring acute hepatotoxicity. It promises a noninvasive, real-time liver-function monitoring method.

Keywords Acetaminophen, Hepatotoxicity, Pulse Analysis, SGOT, SGPT

Most drugs and toxic chemicals are metabolized in the liver, and these processes may cause liver injuries. All the hepatotoxicity monitoring methods include histopathological evidence, and the blood liver function indexes that examine serum glutamate pyruvate transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) are invasive and time-consuming; they can hardly alert one to a drug-induced fulminant hepatic failure in time to save the liver.

The pulse analysis, a noninvasive, real-time liver-function monitoring method is presented in this article. It is based on the resonance theory we first proposed in 1989 (Wang et al. 1989; Wang Lin et al. 1991). According to this theory, each organ or tissue, with its entity as an arterial tree, is coupled with the main artery and undergoes forced oscillations that have selective frequencies. The physical condition of the organ is the main factor that influences the coupling status. Since the entire arterial system is a combination of all the organ–main-artery coupling units, the pressure wave of the arterial system will reflect the physical condition of all the organs. Experimental evidence indicates that the physical condition of organs is related to different Fourier components of the pressure pulse. We found that the amplitude of the second harmonic of the pressure-wave spectrum would drop significantly during renal artery ligation, while the amplitude of the third harmonic would drop significantly during spleen artery ligation (Wang Lin et al. 1991, 1997; Young et al. 1989, 1992; Yu et al. 1994). Investigation of the pulse spectrums of hospital patients with acute uncomplicated myocardial infarction indicated

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that the heart is related to the DC term (the average height or intensity of the original pulse of the pressure spectrum (Chen et al. 1993)). Studies of chemical-factory workers with abnormal blood tests (Wang et al. 1996) and of hospital patients with possible liver problems (Lu et al. 1996) found that the abnormal level of intensity of the first harmonic of the pressure-wave spectrum was highly correlated with abnormal values of the liver indexes SGPT, SGOT, bilirubin, and so on.

During a drug-induced fulminant hepatic failure, SGPT and SGOT are usually the first tests used to check liver function, for they're relatively convenient and time-saving, compared to other methods such as the histological method. Although we still cannot absolutely exclude the possibility of poor liver function at low levels of SGPT and SGOT, the abnormally high levels of SGPT and SGOT do indicate possible liver failure, so emergency action can be taken immediately. There are great advantages when the noninvasive pulse analysis method can be used as a real-time, first-line indicator. It is possible to monitor the hepatic toxicity level as frequently as desired and to read the results instantly. For this purpose, dose/response SGPT and SGOT values were studied in Wistar rats given massive doses of acetaminophen (APAP), and the correlation between the amplitude of the first harmonic of the blood pressure (BP) pulse, A1, and the SGPT and SGOT levels was studied. APAP in dimethyl sulfoxide (DMSO) was given by multiple injections 5 h apart to minimize the injection volume, avoid single-dose toxicity, reduce mortality, and effectively build up the dose/response values of SGPT and SGOT.

APAP was chosen because it is inexpensive, readily available, and has a low operating danger. This analgesic and antipyretic drug is safe at therapeutic doses, but it can cause severe liver damage at the level of overdose (Nelson 1990; Prescott 1983). Because APAP-induced hepatotoxicity is less severe in rats than in humans (Davis et al. 1974), massive APAP doses (>1 g/kg) are needed to build up a significant increase in serum levels of SGPT and SGOT. A huge volume has to be delivered if the drug is carried by saline (Echard et al. 2001; Kostrubsky et al. 1995; Tarloff et al. 1996). Nonetheless, to keep the pulse studies faithful, the injection volume should be minimized so as to avoid disturbance of the blood circulation. Therefore, DMSO was chosen as the carrier of APAP for its high solvency. APAP in DMSO given by multiple injections was proven to effectively induce fulminant acute hepatic failure in dogs (Francavilla et al. 1989). There have been reports that DMSO might protect against acetaminophen-induced hepatotoxicity somewhat (Jeffery and Haschek 1988; Park et al. 1988); we may, therefore, have faced lower mortality rates or less elevation of SGPT and SGOT values for the same amount of APAP by using DMSO as the carrier. However, this just adds more space between safety and death when studying the APAP dose response. Other advantages of using DMSO include the small injection volume, the trustable dosage, and the steady absorption rate, all keys to a successful result.

A single dose of acetaminophen was not considered because it can result in significant animal mortality that may not be due to hepatic injury but to factors such as methemoglobinemia and cardiorespiratory failure (Cobden et al. 1982; McLean et al. 1967). To effectively build up the levels necessary to examine SGPT and SGOT values, prolonged elevated blood levels of APAP are required (Davis et al. 1974; Jollow et al. 1974). According to studies of male 3-month-old Sprague-Dawley rats (Tarloff et al. 1996), both serum and hepatic APAP concentrations reach the maximum at 2 h following intraperitoneal injection of the drug and then drop slowly over 6 h. Our preexperiment tests (data not shown) found that a 5-h interim between each injection effectively builds up the necessary SGPT and SGOT values and results in a low mortality rate.

MATERIALS AND METHODS

APAP, DMSO, and urethane were purchased from Sigma Chemical (St. Louis, MO). Wistar rats between 220 and 340 g were purchased from the experimental animal center of National Taiwan University (Taipei, Taiwan). A total of 114 rats were divided into seven groups; total APAP doses were 0 (control group); 0 (DMSO group); and 1000, 1500, 2000, 2400, and 3000 mg/kg, respectively.

APAP in DMSO (600 mg/mL) was given as four intraperitoneal injections 5 h apart, with the first dose to be one half and the consecutive three doses to be one sixth of the total dose. We used a larger first dose to build up the serum APAP concentration and the following smaller doses to maintain the level. For the DMSO group, a volume of pure DMSO equal to that given the 3000 mg/kg APAP group was injected. For the naive control group, there was no injection.

Then 12 h after the last injection, the rats were anesthetized with urethane (0.84 g/kg). The tail artery was cannulated with an intravenous catheter (Becton Dickinson Infusion Therapy System Inc., USA) filled with physiological saline and heparin, which was then connected to a pressure transducer (RP-1500 Narco Biosystem, Houston, Texas). The BP pulses in the tail artery were obtained through the transducer, which was in series with a preamplifier, an A/D converter, and an IBM PC. (Yu et al. 1994)

After cannulation, 210 min were allowed for stabilization. Then every 2 min, we recorded one pressure-wave sequence for 1 sec, which contained 5 to 7 consecutive pulses. A total of 45 pressure-wave sequences were taken in 90 min. Then 1 mL of blood was drawn for liver function index (SGPT and SGOT) analysis. Each pulse in the pressure-wave sequence was separated at the lowest point (the place where diastolic pressure (DP) started) and the DC trend was corrected. The separated pulses were Fourier-transformed into the frequency domain, and the amplitude of the first harmonic, A1, was calculated.

The A1 of all the recorded pulses in 210–300 min were averaged. The physiological indexes (BP = systolic pressure (SP) − diastolic pressure (DP)) were recorded and averaged also. The quality of the data was monitored according to the BP; if it was higher than 30 mmHg it was considered to be data. Either the toxicity had severely affected the cardiovascular system, or

blood clots in the intravenous catheter had caused the large drop in BP.

A blood test was used as the gold standard. The validity of the pulse-spectrum analysis was evaluated by the kappa value and X^2 test (chi-square test).

RESULTS

Table 1 shows all the data averaged from all of the surviving rats with BP higher than 30 mmHg; there were 25 control rats; 11 given DMSO; 21 given 1000 mg/kg; 10 given 1500 mg/kg; 9 given 2000 mg/kg; 8 given 2400 mg/kg; and 9 given 3000 mg/kg. Table 1 shows that the average values of SGPT and SGOT increased with the APAP doses. The average value of the liver function index of the BP pulse spectrum A1 was significantly decreased when the APAP dose was larger than 1500 mg/kg. The A1 drop in the DMSO control group is to be noted. We found that the DMSO group had higher average DP and SP values than the control group and the 1000 mg/kg group. However, the averaged DP and SP values increased with higher dosages and reached the maximum at 2000 mg/kg. The mortality rate at 5 h after urethane injection was zero for the rats given doses of 1500 mg/kg and less and was 7 of 18 for the rats given 2400 or 3000 mg/kg. There were higher survival rates in the rats with huge BP drops in these two groups, too. When the DMSO set was compared, the DP, SP, and BP variations in all the APAP sets were insignificant except for the rats given 1000 mg/kg.

Table 2 gives the kappa and X^2 test results of the SGPT and SGOT, and liver-function indexes of the BP pulse spectrum A1. When A1 was lower than 3650, the probability that SGPT was higher than 90 and that SGOT was higher than 380 was greater than .999, based on a chi-square test. The kappa value of SGPT–A1 was close to the substantial level; it was lower for the SGOT–A1 relationship.

Table 3 considers high DP (>90 mmHg) as an additional condition together with low A1 (<3650). If a rat had A1 lower

TABLE 1
The averaged data and the statistical results for rats with BP = systolic-diastolic >30 mmHg

Dose	Control	DMSO	1000 mg/kg	1500 mg/kg	2000 mg/kg	2400 mg/kg	3000 mg/kg
A1	3769	3657	3840	3672	3385	3417	3443
SE	22	34	20	61	61	48	98
		**	*		***	***	**
			†††		††	†††	†
SGPT	58.4	64.4	64.0	84.5	89.6	149	140
SE	3.7	9.8	4.7	10.1	13.3	20.6	16.6
				*	*	**	***
				†	†	††	†††
SGOT	295	273	299	305	381	510	490
SE	15.6	30	20	28	46	53	35
						**	***
					†	††	†††
DP (mmHg)	78.9	86.1	78.8	85.6	91.3	89.4	83.8
SE	1.4	2.8	1.5	2.3	3.5	3.6	3.1
		*		*	**	*	
			†				
SP (mmHg)	129.2	131.4	124.2	129.8	140.1	133.9	127.2
SE	1.7	3.3	1.8	3.1	3.5	3.6	2.7
			*		*		
			†				
BP (mmHg)	50.3	45.2	43.9	44.2	48.2	44.4	43.1
SE	0.6	1.2	1.2	2.2	2.2	1.7	3.1
		**	***	*		**	*
HR (Hz)	6.9	6.8	6.8	6.9	7.0	7.3	7.5
SE	0.1	0.2	0.1	0.1	0.2	0.3	0.3
Mortality[a]	0/25	0/12	0/21	0/10	1/10	7/18	7/18

[a]Mortality, mortality at 5 h after urethane injection; SE, standard error.

Note: The t-test probabilities of significant difference between each dose set with the naive control set are given as $^{*}p > .95$; $^{**}p > .99$; $^{***}p > .999$.

The t-test probabilities of significant difference between each dose set with the DMSO set are given as $^{\dagger}p > .95$; $^{\dagger\dagger}p > .99$; $^{\dagger\dagger\dagger}p > .999$.

TABLE 2
The kappa and X^2 test results of SGPT, SGOT, and the liver-function index of the BP pulse spectrum A1

	SGPT > 90	SGPT < 90	Total
A1 > 3650	6 (18)	52 (40)	58
A1 < 3650	23 (11)	12 (24)	35
Total	29	64	93

$X^2 = 31.18$; $p < .0001$; $\kappa = 0.573$.

	SGOT > 380	SGOT < 380	Total
A1 > 3650	7 (17)	51 (41)	58
A1 < 3650	21 (11)	14 (24)	35
Total	28	65	93

$X^2 = 23.83$; $p < .0001$; $\kappa = 0.499$.
Note: The numbers in parentheses are the expected values.

TABLE 4
The kappa and X^2 test results of SGPT, the liver-function index of the BP pulse spectrum A1, and the DP

	SGPT > 90	SGPT < 90	Total
DP < 90	13 (22)	58 (49)	71
DP > 90	16 (7)	6 (15)	22
Total	29	64	93

$X^2 = 23.18$; $p < .0001$; $\kappa = 0.490$.

	A1 < 3650	A1 > 3650	Total
DP < 90	18 (27)	53 (44)	71
DP > 90	17 (8)	5 (14)	22
Total	35	58	93

$X^2 = 19.29$; $p < .0001$; $\kappa = 0.431$.
Note: The numbers in parentheses are the expected values.

than 3650 or DP higher than 90 mmHg for more than 60 minutes, the probability that SGPT would be higher than 90 and that SGOT would be higher than 380 was greater than .999, based on a chi-square test. Along with this DP, the X^2 and kappa values were both increased in the SGPT–A1 correlation, and the kappa value reached the substantial level ($\kappa = .614$). There was no improvement in the SGOT–A1 correlation.

As shown in Table 4, the kappa value of DP–SGPT was .490 when the DP was higher than 90 mmHg and the SGPT was also above 90; the kappa value of DP–A1 was .431 when the DP was higher than 90 mmHg and A1 was below 3650. These values are lower than the kappa value for the SGPT–A1 correlation.

TABLE 3
The kappa and X^2 test results of SGPT, SGOT, and the liver-function index of the BP pulse spectrum A1 as well as diastolic pressure

	SGPT > 90	SGPT < 90	Total
A1 > 3650	3 (17)	50 (36)	53
A1 < 3650 or DP > 90 at more than 60 min	26 (12)	14 (28)	40
Total	29	64	93

$X^2 = 37.41$; $p < .0001$; $\kappa = 0.614$.

	SGOT > 380	SGOT < 380	Total
A1 > 3650	6 (16)	47 (37)	53
A1 < 3650 or DP > 90 at more than 60 min	22 (12)	18 (28)	40
Total	28	65	93

$X^2 = 20.67$; $p < .0001$; $\kappa = 0.453$.
Note: The numbers in parentheses are the expected values.

DISCUSSION

Fulminant hepatic failure can result from an overdose of a drug taken in a short time or can develop from long-term hepatic injury resulting from a variety of causes. It is difficult to predict its onset but it is vital to do so in humans, so it would be a great advantage if we could be alerted and thus able to take action earlier; a more convenient and comfortable method of assessment is needed. Comparing the commonly used first-line liver function indicators SGPT and SGOT, we have shown that the pulse analysis method is a promising one. When the liver function index of the BP pulse spectrum A1 is lower than 3650, there are significantly high probabilities that SGPT is greater than 90 and SGOT is greater than 380, based on a chi-square test.

As an indictor of liver cell damage, it is well known that SGPT is more specific than SGOT. We have seen that the kappa value of the A1–SGPT relationship is much higher than the kappa value of the A1–SGOT relationship. The higher correlation of A1 with the more specific liver function index SGPT might imply a high specification of A1 in liver function too.

Many of the cases in Table 3 have very high DP values (>90 mmHg). If we take the high DP (>90 mmHg) as an additional condition, together with the low A1 (<3650), to test the probability that SGPT is above 90, the kappa value moves to a substantial level ($\kappa = 0.614$). The high DP could be a physiological feedback response that is compensating for the decreasing blood supply to the liver caused by the hepatotoxicity. To avoid occasional nervous responses, only those rats with DP above 90 mmHg for more than 60 min were considered to have real hypertension related to hepatotoxicity.

Since the kappa value of the SGPT–DP relationship is 0.490, and the kappa value of the A1–DP relation is only 0.431, the increase in DP cannot be responsible for the A1–SGPT correlation but can be considered an additional criterion of it only.

The pulse analysis method described in this experiment is to be used to monitor cases in which there is an abnormal

blood supply to the liver but no serious signs of cardiovascular problems. Patients with serious cardiovascular problems; usually including abnormal BP or heart rate, would be easily monitored in a clinical situation. Therefore, only the rats that survived for 5 h after being injected with urethane and had SP–DP higher than 30 mmHg were analyzed.

Compared to the naive control group, the statistically significant effects on the A1, DP, and BP in the DMSO control group have been noted; the physical situation of the circulation system may have been altered somewhat by the relatively large volume of high-density DMSO we injected. The DMSO control group was given a volume of pure DMSO equivalent to the 3000 mg/kg of APAP given that group. Because it has less injection volume, DMSO should have less effect on the groups given 1000 to 2400 mg/kg APAP. Compared with the DMSO group, the statistically significant effects on A1, SGPT, and SGOT in the groups given 2000 to 3000 mg/kg are still valid; nonetheless, the effects on DP, SP, and BP became insignificant in these groups. If saline had been used as the carrier of the APAP, due to the low solvency the injection volume would have been 10-fold greater, the huge injection volume will disturb the blood circulation and we would have faced a more confusing situation.

Since the abnormally high levels of SGPT and SGOT do indicate possible liver failure, regardless of the liver toxicity induced by APAP, solved in DMSO was not fully characterized, stable dose/response SGPT and SGOT values were built into this study to give different liver damage levels. The very high SGPT (>300) and SGOT (>600) values were rarely observed in this study in rats that survived for 5 h after the injection of urethane. Although the blood samples from some dying rats gave higher SGPT (~500) and SGOT (~800) values, these values are much lower than those reported in other animal species. Either APAP-induced hepatotoxicity is less severe in Wistar rats or the DMSO protected them. The mortality rate was lower in this study also; the animals were used more efficiently.

The pulse spectrum A1 may be related to the blood supply to the liver or to blood vessel conditions in the liver; it might have undergone high-speed variations. The SGPT is directly related to cell damage in the liver. These two indexes were well correlated in circumstances of severe hepatotoxicity as indicated by high SGPT and SGOT values, but they may be discrepant in situations of minor toxicity. For example, a drop in the A1 value may lead to a rise in the SGPT and SGOT values hours or days. To cause cell damage usually takes a much longer time than the physiological response of the liver blood flow variation in minor toxicity situations.

The average SGPT value was statistically normal but the A1 value was higher than control at a dose of 1000 mg/kg. With higher doses of APAP (>1000 mg/kg), the average A1 dropped as the dose of APAP increased. This kind of biphasic drug response is common (Altura et al. 1996; Ben-Ami et al. 1991; Cellier et al. 1997). A dose of 1000 mg/kg may be in the tolerable, or pretoxic, stage. In this stage, the circulation system and the liver have not yet been injured, and more blood may be delivered to the liver to metabolize the drug as a normal physiological response. This would explain why, at a dose of 1000 mg/kg, the A1 level increased but the SGPT and SGOT responses did not. At higher doses, when physical injury of the liver had occurred, the resonance became worse and worse, and the decrease in the A1 level was accompanied by an increase in the SGOT and SGPT levels. No A1 effect was seen at 1500 mg/kg; it might be a balance point, at which the increase and decrease in the A1 level was just balanced at that dose. This suggests that we can actually take advantage of this phenomenon: in cases of minor poisoning we may monitor the A1 increase.

As mentioned earlier, the A1 variation represents a change in the physical status of the liver. Therefore, other liver tests may also correlate with changes in the A1 as long as the tested index is related to the physical status of the liver. Just as SGPT and SGOT are not sufficient for liver disease testing, some other harmonics may also play a minor role, together with the A1, in indicating liver disease. Our previous studies (Lu et al. 1996; Wang et al. 1996) have indicated that for chronic liver abnormality testing we may get a better correlation if there is a more complex cross-study between the A1 and other minor harmonics of liver disease testing such as bilirubin, alkaline phosphates, and cholesterol levels, ultrasound scans, and so on.

The APAP may induce damage that has various aspects; further studies are needed to clarify the A1 relationship with the toxicological effects on organs other than the liver. Nonetheless, based on organ ligation experiments (Wang Lin et al. 1991; Young et al. 1989, 1992; Yu et al. 1994), studies of chemical-factory workers with abnormal blood tests (Wang et al. 1996), hospital patients with possible liver problems (Lu et al. 1996), and patients with acute uncomplicated myocardial infarction (Chen et al. 1993), all the evidence indicates that the physical condition of various organs is specifically related to the Fourier components of the pressure pulse as a first approximation. It infers that the liver is specifically related to A1, although it may also have a minor cross-relation to other harmonics.

This preliminary study was aimed at the comparison between A1 with the commonly used blood indexes SGPT and SGOT. The correlation between the A1 and the SGPT and SGOT levels indicates that the amplitude of the first harmonic of the pressure pulse spectrum is a noninvasive indicator that may hold a diagnosis position similar to that of SGPT and SGOT when screening for liver toxicity initially. In humans, we may easily record the BP waves from the radial artery on the wrist by using a noninvasive pressure transducer. It may be a leading index; it may alert clinicians to the hepatotoxic status well before any severe damage begins.

REFERENCES

Altura, B. M., Zou, L. Y., Altura, B. T., Jelicks, L., Wittenberg, B. A., and Gupta, R. K. 1996. Beneficial vs. detrimental actions of ethanol on heart and coronary vascular muscle: roles of Mg super(2+) and Ca super(2+). *Alcohol* 13:499–513.

Ben-Ami, H., Ben-Haim, S. A., Edoute, Y., Hayam, G., and Taitelman, U. 1991. Direct effects of phosphamodion on isolated working rat heart electrical and mechanical function. *Toxicol. Appl. Pharmacol.* 110:429–434.

Cellier, E., Barbot, L., Regoli, D., and Couture, R. 1997. Cardiovascular and behavioural effects of intracerebroventricularly administered tachykinin NK sub(3) receptor antagonists in the conscious rat. *Br. J. Pharmacol*. 122:643–654.

Chen, C. Y., Wang, W. K., Kao, T., Chen, B. C., and Chiang, C. 1993. Spectral analysis of radial pulse in patients with acute uncomplicated myocardial infarction. *Jpn. Heart. J*. 34:37–49.

Cobden, I., Record, C. O., Ward, M. K., and Kerr, D. N. 1982. Parcetomol-induced acute renal failure in the absence of fluminant liver disease. *Br. Med. J. (Clin. Res. Ed.)* 284:21–2.

Davis, D. C., Potter, W. Z., Jollow, D. J., and Mitchell, J. R. 1974. Species differences in hepatic glutathione depletion, covalent binding and hepatic necrosis after acetaminophen. *Life Sci.* 14:2099–2109.

Echard, B. W., Talpur, N. A., Fan, A. Y., Bagchi, D., and Preuss H. G. 2001. Hepatoprotective ability of a novel botanical formulation on mild liver injury in rats produced by acute acetaminophen and/or alcohol ingestion. *Commun. Mol. Pathol. Pharmacol*. 110:73–85.

Francavilla, A., Makowka, L., Polimeno, L., Barone, M., Demetris, J., Prelich, J., Van Thiel, D. H., and Starzl, T. E. 1989. A dog model for acetaminophen-induced fluminant hepatic failure. *Gastroenterology* 96:470–478.

Jeffery, E., and Haschek, W. 1988. Protection by dimethysulfoxide against acetaminophen-induced hepatic, but not respiratory toxicity in the mouse. *Toxicol. Appl. Pharmacol*. 93:452–461.

Jollow, D. J., Thorgiersson, S. S., Potter, W. A., Hashimoto, M., and Mitchell, J. R. 1974. Acetaminophen-induced hepatic necrosis. VI: Metabolic disposition of toxic and nontoxic doses of acetaminophen. *Pharmacology* 12:251–271.

Kostrubsky, V. E., Wood, S. G., Bush, M. D., Szakacs. J., Bement, W. J., Sinclair, P. R., Jeffery, E. H., and Sinclair J. F. 1995. Acute hepatotoxicity of acetaminophen in rats treated with ethanol plus isopentanol. *Biochem. Pharmacolo*. 50:1743–1748.

Lu, W. A., Cheng, C. H., Wang Lin, Y. Y., and Wang, W. K. 1996. Pulse spectrum analysis of hospital patients with possible liver problems. *Am. J. Chin. Med*. 24:315–320.

McLean, S., Murphy, B. P., Starmer G. A., and Thomas, J. 1967. Methaemoglobin formation induced by aromatic amines and amides. *J. Pharm. Pharmacol*. 19:146–154.

Nelson, S. D. 1990. Molecular mechanisms of the hepatotoxicity caused by acetaminophen. *Semin. Liver Dis*. 10:267–268.

Park, Y., Smith, R. D., Combs, A. B., and Kehrer, J. P. 1988. Prevention of acetaminophen-induced hepatotoxicity by dimethy sulfoxide. *Toxicology* 52:165–175.

Prescott, L. F. 1983. Paracetamol overdosage: pharmacological considerations and clinical management. *Drugs* 25:290–334.

Tarloff, J. B., Khairallah, E. A., Cohen, S. D., and Goldstein, R. S. 1996. Sex- and age-dependent acetaminophen hepato- and nephrotoxicity in Sprague-Dawley rats: role of tissue accumulation, nonprotein sulfhydryl depletion, and covalent binding. *Fundam. Appl. Toxicol*. 30:13–22.

Wang Lin, Y. Y., Chang, C. C., Cheng, J. C., Hsiu, H., and Wang, W. K. 1997. Pressure wave propagation in arteries: a model with radial dilatation for simulating the behavior of a real artery. *IEEE Engin. Med. Biol*. Jan./Feb.:51–56.

Wang Lin, Y. Y., Chang, S. L., Wu, Y. E., Hsu, T. L., and Wang W. K. 1991. Resonance: the missing phenomena in hemodynamics. *Circ. Res*. 69:246–249.

Wang, W. K., Lo, Y. Y., Chiang, Y., Hsu, T. L., and Wang Lin, Y. Y. 1989. Resonance of organs with the heart. In *Biomedical Engineering: An International Symposium*, ed. W. J. Young, 259–268. Washington, D.C: Hemisphere.

Wang, W. K., Tsuei, J., Chang, H. C., Hsu, T. L., and Wang Lin, Y. Y. 1996. Pulse spectrum analysis of chemical factory workers with abnormal blood test. *Am. J. Chin. Med*. 24:199–203.

Young, S. T., Wang, W. K., Chang, L. S., and Kao, T. S. 1989. Specific frequency properties of the renal and the supermesenteric arterial beds in rats. *Cardiovas. Res*. 23:465–467.

Young, S. T., Wang, W. K., Chang, L. S., and Kao, T. S. 1992. The filter properties of the arterial beds of organs in rats. *Acta Physiol. Scand*. 145:401–406.

Yu, G. L., Wang Lin, Y. Y., and Wang, W. K. 1994. Resonance in the kidney system of rats. *Am. J. Physiol. (Heart Circ. Physiol.)* 36:H1544–H1548.