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The in Vitro and in Vivo Effects of Extracorporeal Shock Waves on Malignant Cells*

R. F. Randazzo[1], C. G. Chaussy[1], G. J. Fuchs[1], S. M. Bhuta[2], H. Lovrekovich[1], and J. B. deKernion[1]

[1]Department of Surgery, Division of Urology, and [2]Department of Pathology, UCLA School of Medicine, Los Angeles, California, United States of America

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Summary. The in vitro cytotoxic effect of extracorporeal shock waves (ESW) on renal cell carcinoma (RCC) cells was compared to the effect on normal human embryonic kidney (NHEK) cells. In the in vitro studies cell samples were brought into the second focal point and exposed to different numbers of shock wave impulses. The four parameters of RCC tumor cell injury which were measured, i.e., cell viability, cell growth, cell attachment and electron microscopic evidence of damage, were augmented with increasing SW levels. At 2,000 shock waves (SW) a significant decrease in RCC viability, cell growth and cell attachment was seen compared to the NHEK cells. In the in vivo experiment a FANFT induced bladder tumor was transplanted into the right hind legs of C3H/He mice and the tumors were exposed to 1,400 SW. Preliminary data showed that 1,400 SW at day 12 post transplant significantly inhibited tumor growth. Combining 1,400 SW with cis-diamminedichloroplatinum (4 mg/kg) did not enhance the tumor inhibitory effect of each individually. Doxorubicin (5 mg/kg) and 1,400 SW produced a significant synergistic tumor inhibitory effect.

Key words: Extracorporeal shock waves – Renal cell carcinoma – Bladder cancer – Renal embryogenic cells

Introduction

In the first in vitro experiments involving shock waves, lymphocytes in cultures were exposed to different levels of shock waves. No cytotoxicity or inhibition of mitogen stimulation was noted [1]. After six years of experimental studies which excluded a significant cytotoxic effect on normal cells, extracorporeal shock waves (ESW) were first introduced into clinical medicine in 1980 by Chaussy et al. [2]. At that time it was shown that ESW could disintegrate renal and ureteral calculi. Since the over 80,000 patients have been treated with minimal morbidity.

The effects of shock waves on tumor cells was first investigated by Russo, et al. Using the Dunning R3327AT-3 rat anaplastic prostatic carcinoma and SK-Mel-28 human melanoma cell lines they showed that ESW can inhibit both in vitro and in vivo tumor cell growth [4].

The experiments herein reported investigate the in vitro and in vivo effects of ESW on malignant cells. In the in vitro experiments the effects of extracorporeal shock waves on renal carcinoma cells were compared to the effects on normal human embryonic kidney cells. A mouse bladder tumor (MBT) transplanted into C3H/He mice was used in the in vivo experiments [3]. The effects of shock waves in the in vivo system were combined with cisplatinum and doxorubicin.

Materials and Methods

In Vitro Cell Cultures

A renal cell carcinoma (RCC) cell line, RcPa, isolated in our laboratory and a normal human embryonic kidney cell line (NHEK) (Flow Labs, Inglewood, CA) were used. The RCC cell line was between the 110th to the 122th passage and the NHEK cell line was between the 16th to the 22th passage. Both cell types were maintained at 37 degrees C with 5% carbon dioxide in T250 tissue culture flasks with RPMI 1640 medium containing 10% fetal calf serum and antibiotics. The tissue culture cells were dissociated with trypsin, 0.25%, (Flow Labs.) for 4–5 min, washed with PBS, mechanically separated and resuspended in PBS. Viability counting was performed with the trypan blue exclusion technique (final concentration of 0.025%) using a hemocytometer. 2 ml suspensions containing 1×10^7 cells/ml were made of each cell type and placed in polypropylene test tubes. The cell suspensions were either placed in the bath of the extracorporeal shock wave machine (human model 3, Dornier, Munich, Germany) outside of the focus (control) or in the second focal point. An antenna was secured to the undersurface of the support system of the machine's gantry. The antenna was designed so that its tip was in the center of the second focus. The tubes were secured to the antenna with plastic adhesive.

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In Vitro Protocol

Using 18 kV and 100 shocks/min, the experimental suspensions were exposed to either 800, 1,400 or 2,000 shock waves (SW). The experiment was repeated 6 times for the RCC cells and 3 times for the NHEK cells. Each electrode was used for 800 SW.

Following SW treatment an aliquot of each specimen was taken and viability again determined with trypan blue ($n = 8$ for RCC cells and $n = 6$ for NHEK cells). 3.36×10^6 viable cells were taken from each experimental group and placed into triplicate tissue culture flasks as above and cultured for one, two or five days. After cell culture the cells were harvested with trypsin, mechanically separated, and washed in PBS as above. Cells which were free floating in the medium before trypsinization were classified as detached cells. Cells adherent to the tissue culture flasks were classified as attached cells. Cell counts, percent of cell attached and viabilities of both attached and detached cells were performed at 24, 48 and 120 h. All cell counts were performed with a Hycel cell counter (Boehringer Mannheim, Houston, Texas).

In order to evaluate the long term in vitro effects of SW on cell proliferation, the cell growth was determined after the first and second tissue culture passage. This was done by taking 5×10^5 viable cells from each treatment group after the original five days of tissue culture and then resuspending these cells, placing them back into tissue culture and growing them for an additional seven days.

Viability and cell counts were done after seven days of growth. This constituted the growth of shock wave treated cells after the first passage. The same procedure was used to determine the growth of cells after the second passage. Two experiments were done with each cell type after the first and second passage.

Electron Microscopic Studies

Cell cultures were prepared using the same method as above for electron microscopic (EM) study. The EM experiments were repeated three times for the RCC cells and twice for the NHEK cells. The EM fixative contained 2.0% paraformaldehyde, 2.5% glutaldehyde and 0.1 M cacodylate with 7.2 pH. After fixation, the cells were washed twice in buffered 0.1 M cacodylate and fixed again in 1% osmium tetraoxide. Ultrathin sections were stained with uranyl acetate and lead citrate. EM evaluation was performed immediately after SW (0 h), 48 and 120 h later. For the 0 h studies, the cells were exposed to SW, viability performed and the cells immediately placed into the EM fixative. For the 48 and 120 h EM studies, the cells were SW treated, placed back into cell culture for 48 or 120 h and the attached cells were harvested and placed into the EM fixative.

In Vivo Cell Lines

The tumor cell line, MBT, was originally derived from an invasive transitional cell carcinoma induced in female C3H/He mice who had chronically ingested a carcinogen named N-[4-(5-nitro-furyl)-2-thiazolyl], FANFT. Single cell suspensions of the tumor were prepared according to the method of deKernion et al. with modification to a single trypsinization step [3].

Experimental Animals

5×10^5 FANFT bladder tumor cells were injected into the right hind legs of C3H/He mice, 8–10 weeks old, female (Simonson Labs, Gilroy, CA). Within 7 days palpable tumors were present. Measurements of the maximum perpendicular tumor diameters were taken three times a week with a Vernier caliper. Median survival time was also monitored.

In Vivo Protocol

For the shock wave treatment of the mice a protective capsule was constructed which consisted of a inner plastic tube with a 3 mm thick protective styrofoam covering. The capsule had a hole on the side near the bottom which allowed the right hind leg to exit. The capsule was attached to a wedge which was in turn secured to the vertical antenna. The angle of the capsule to the vertical was 60 degrees.

All animals were anesthetized with an intraperitoneal injection of sodium pentobarbitol 60 mg/kg. The experimental animals were placed in the capsule with the tumor in the second focus. Two fine wires were placed around the tumor for localization. The control animals were placed on the seat of the chair which was 16 inches from the second focus. The energy level was 18 kV for the first two experiments and 20 kV for the third with 100 shocks/min in all experiments.

All animals were randomly divided into control or experimental groups. In the first experiment the right hind leg was exposed to either 0 SW ($n = 9$), 800 SW ($n = 8$), 1,400 SW ($n = 5$) at day 12 after tumor inoculation.

In the second experiment, ESW and cis-diamminedichloroplatinum (CDDP) were combined. The four groups used were: control ($n = 9$), CDDP (4 mg/kg) alone ($n = 8$), CDDP (4 mg/kg) and 1,400 SW ($n = 8$) and 1,400 SW alone ($n = 5$). The CDDP was given i.p. in 0.5 cc at day 6 and then once a week thereafter for three weeks. 1,400 SW was given at day 12.

In the third experiment, ESW and doxorubicin were combined. The four groups used were: control ($n = 30$), doxorubicin (5 mg/kg) alone ($n = 20$), 1,400 and doxorubicin (5 mg/kg) combined ($n = 20$ before ESW and $n = 9$ after ESW) and 1,400 SW alone ($n = 20$ before ESW and $n = 9$ after ESW). Doxorubicin 5 mg/kg was given i.p. in 0.5 cc at day 6 and once a week thereafter for three additional weeks. 1,400 SW was given at either day 12 or day 17.

The data for the in vitro experiment was analyzed with the unpaired two-tailed Student-t test for discrete sample populations and linear regression for cell growth rates and percent cell attachment. Student-t test was used for the in vivo experiments. $P < 0.05$ was considered significant.

In Vitro Results

Viability. Viability by trypan blue after ESW was dose-related with increasing shock wave levels resulting in decreasing viability. The RCC cells had a lower viability than the NHEK cells at each level of ESW. There was a significant decrease in viability for the RCC cells, 66 ± 3.3, compared to NHEK cells, 79 ± 2.5, at 2,000 SW ($p < 0.05$) (Fig. 1).

Cell Growth. A dose-related effect was also seen on the RCC and NHEK cell growth rates over the first five days, with a significant difference in cellular growth rate between the control and each experimental group within each cell type. The RCC cells had a decreased growth rate compared to the NHEK cells at each SW level (Fig. 2). However, the RCC growth was significantly less than that of the NHEK cells only at 2,000 SW, $p < 0.001$ (Fig. 2d).

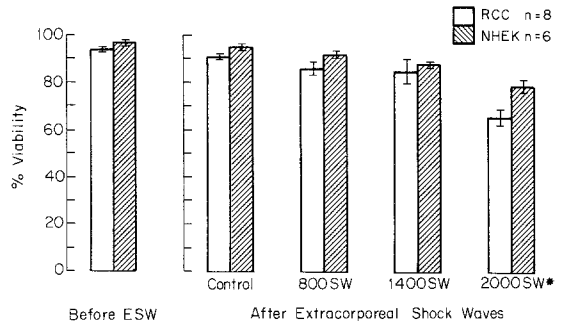

Fig. 1. Viabilities of cell cultures before and after different levels of extracorporeal shock waves (ESW). RCC = Renal cell carcinoma cells. NHEK = Normal human embryonic kidney cells. * $p < 0.05$

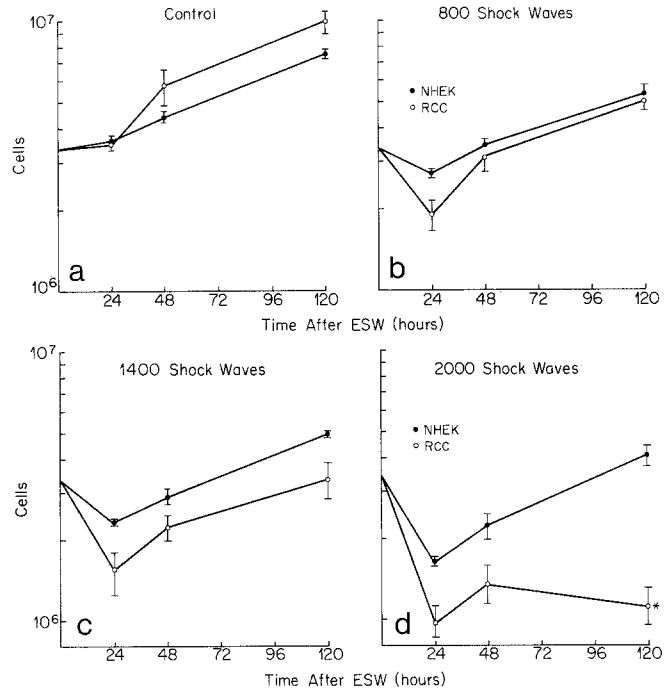

Fig. 2a–d. Comparison of cell growth between ○ RCC and • NHEK cells after the following levels of ESW. a control, b 800 SW, c 1,400 SW and d 2,000 SW. * $p < 0.001$

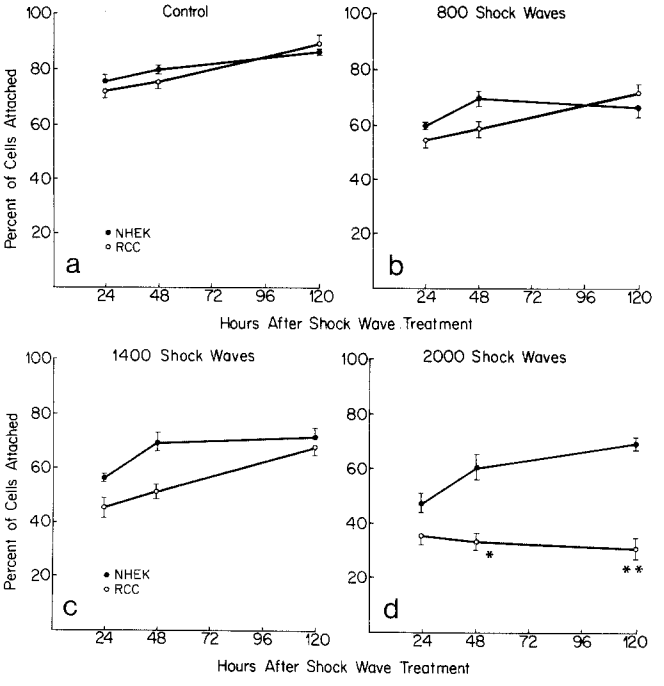

Fig. 3a–d. Comparison of percent of cells attached after ESW. a control, b 800 SW, c 1,400 SW and d 2,000 SW. ○ RCC and • NHEK. * $p < 0.05$, ** $p < 0.001$

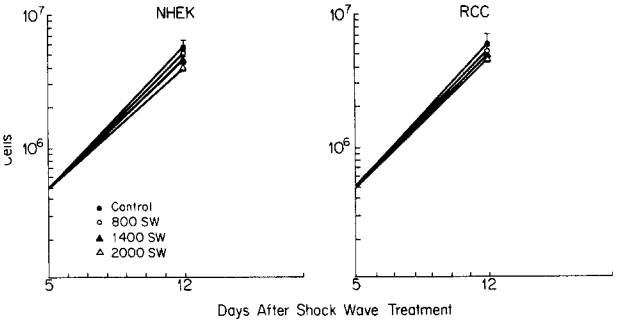

Fig. 4. Growth rate of shock wave treated cells after the first passage. • control, ○ 800 SW, ▲ 1,400 SW and △ 2,000 SW

Cell Attachment. Cell attachment was determined at 24, 48 and 120 h after shock wave exposure by dividing the number of attached cells by the total number of cells in the flask (attached and detached). Once again there was a dose-related decrease in the cell attachment. When a comparative analysis of each cell type was performed at each level of ESW (Fig. 3), a significant decrease in cell attachment was evident at 2,000 SW for the RCC cells compared to the NHEK cells (Fig. 3d) ($p < 0.05$).

Cell Culture Passages. At day 5 following ESW, 5×10^5 viable, attached cells from each treatment were placed back into culture and grown for 7 days. Figure 4 shows identical cell growth for the four treatment groups of each cell type. This constituted the cell growth after the first passage. Cell growth was also identical for each treatment level for both cell types after the second passage.

EM Study. The following EM results were seen immediately after ESW. In the RCC cells at 1,400 SW, there was segmentation of the nuclei and the mitochondria showed swelling with marked variation in size and shape including megamitochondria. The mitochondrial matrix appeared very electron dense and presented as bands or ribbons with ballooned cristae. Free ribosomes and rough endoplasmic reticulum (RER) were still visualized. Secondary lysosomes and vacuoles were present. The cell contours appeared rounded due to the loss of peripheral cell processes (Fig. 5e).

At 2,000 SW with RCC cells the damage appeared much greater and gradual progression to cellular necrosis was frequently seen. The changes were characterized by nuclear fragmentation and disintegration. Only mitochondrial outlines were seen. Most of the free ribosomes and RER were lost. The cell matrix showed haphazardly distributed cytofilaments. The number of secondary lysosomes

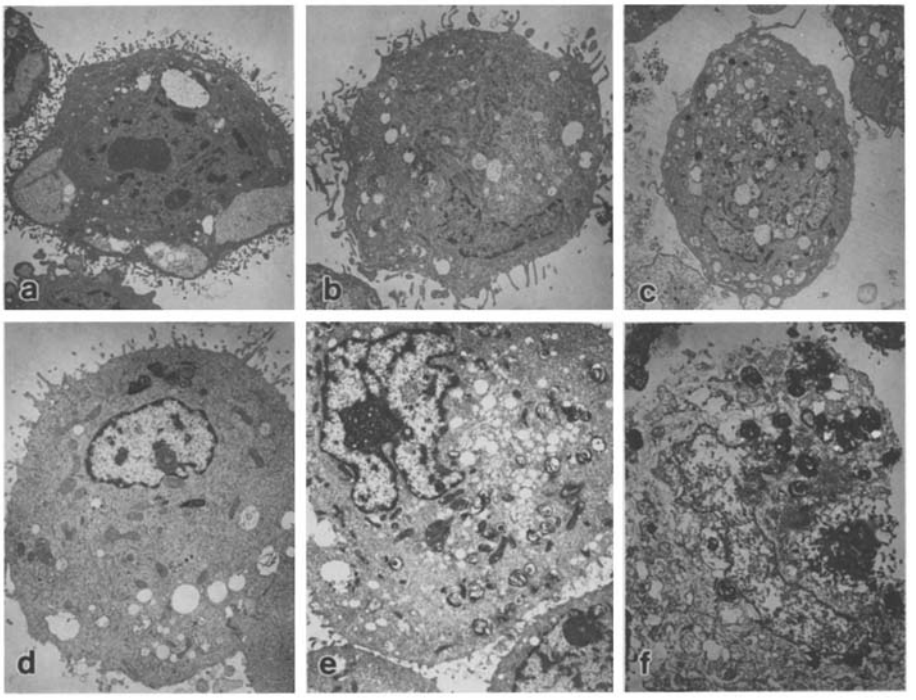

Fig. 5a–f. EM comparison at low magnification (2,800x) between the NHEK cells for **a** control, **b** 1,400 SW and **c** 2,000 SW; and RCC cells for **d** control, **e** 1,400 SW and **f** 2,000 SW

was greatly increased, including many lamellar bodies. Disintegrating cell membranes and debris were present (Figs. 5f and 6b). The changes noted in the NHEK cells are similar but much less pronounced and were seen mainly with high SW levels, i.e., at 2,000 SW (Figs. 5c and 6a).

EM study of both cell types at 48 h after ESW showed no discernible improvement in cell morphology.

At 120 h after ESW with 2,000 SW there was still significant morphologic damage to both NHEK and RCC cells. At 1,400 SW and 120 h there was improvement in ultrastructure in both types with the NHEK cells having much better morphology.

In Vivo Results

Effects of Different Levels of SW. Preliminary experiments showed that ESW given at day 6 after tumor inoculation (prior to a palpable tumor) were ineffective in inhibiting tumor growth even if high levels were used, i.e., 2,000 SW. Subsequent experiments showed that 800 SW given at day 12 or two exposures of 800 SW at day 12 and 16 were also ineffective. Figure 7 shows the dose effect of different levels of SW given at day 12 of the tumor's growth (tumor diameter 8–9 mm). 800 SW, as mentioned, is ineffective; however, 1,400 SW can significantly inhibit tumor growth ($p < 0.05$). A dose-related effect was apparent. 2,000 SW was attempted; however, the mortality rate was 31%.

In these preliminary experiments with 18 kV no mice died from 800 or 1,400 SW. Autopsies of the mice dying after 2,000 SW showed free peritoneal and thoracic blood with hemorrhagic congestion of the lungs. The abdominal and thoracic injuries appear secondary to inadvertent SW exposure despite the protective syrofoam capsule.

1,400 SW was the minimally effective level of shock waves which could inhibit tumor growth. It was used in the subsequent experiments. After the initial tumor inhibition with 1,400 SW, the tumor grew parallel to the control. Because of this, chemotherapeutic agents which were effective in this tumor model were used in combination with SW to see if the SW effect could be potentiated.

Effects of CDDP and 1,400 SW. CDDP (4 mg/kg) alone and 1,400 SW alone given at day 12 both significantly decreased tumor growth (Fig. 8) ($p < 0.001$ and $p < 0.05$ respectively). Combining CDDP and 1,400 SW did not enhance the tumor inhibitory effect of each individually.

The mice receiving CDDP and the combination of CDDP and 1,400 SW were weighted at days 6, 14 and 21 after tumor inoculation. There was no significant difference in weights between these two groups, i.e., in mice receiving CDDP, 1,400 SW did not decrease the mice's weight.

Effects of Doxorubicin and 1,400 SW. Doxorubicin (5 mg/kg) caused a significant decrease in tumor diameter on days 29 and 30 (Fig. 9) ($p < 0.05$). 1,400 SW showed a significant decrease in tumor diameter between days 22 and 30 ($p < 0.05$). If a synergistic effect is defined as a combined effect which is greater than the sum of the two individual effects, then between days 15 and 24 there was a synergistic tumor inhibitory effect between doxorubicin and 1,400 SW (Table 1). Between days 26 to 34 there was almost complete tumor inhibition ($p < 0.001$).

The mice which received doxorubicin alone and those receiving the combination of doxorubicin and 1,400 SW were weighed at days 6, 14, 21 and 28 days after tumor inoculation. There was no weight difference at days 7 and 28; however, a 10% decrease in weight was seen at days 14 and 21 in the group receiving both doxorubicin and 1,400 SW compared to the doxorubicin alone group ($p < 0.05$).

For the doxorubicin experiment the energy level was increased from 18 to 20 kV and the number of shocks per electrode was increased from 800 to 1,000. With these increases, there was a 43% mortality rate in the mice treated with 1,400 SW and doxorubicin and 48% mortality in the 1,400 SW group; however, despite this, there were at least 9 surviving mice in each group. No mice died in the control or doxorubicin alone groups.

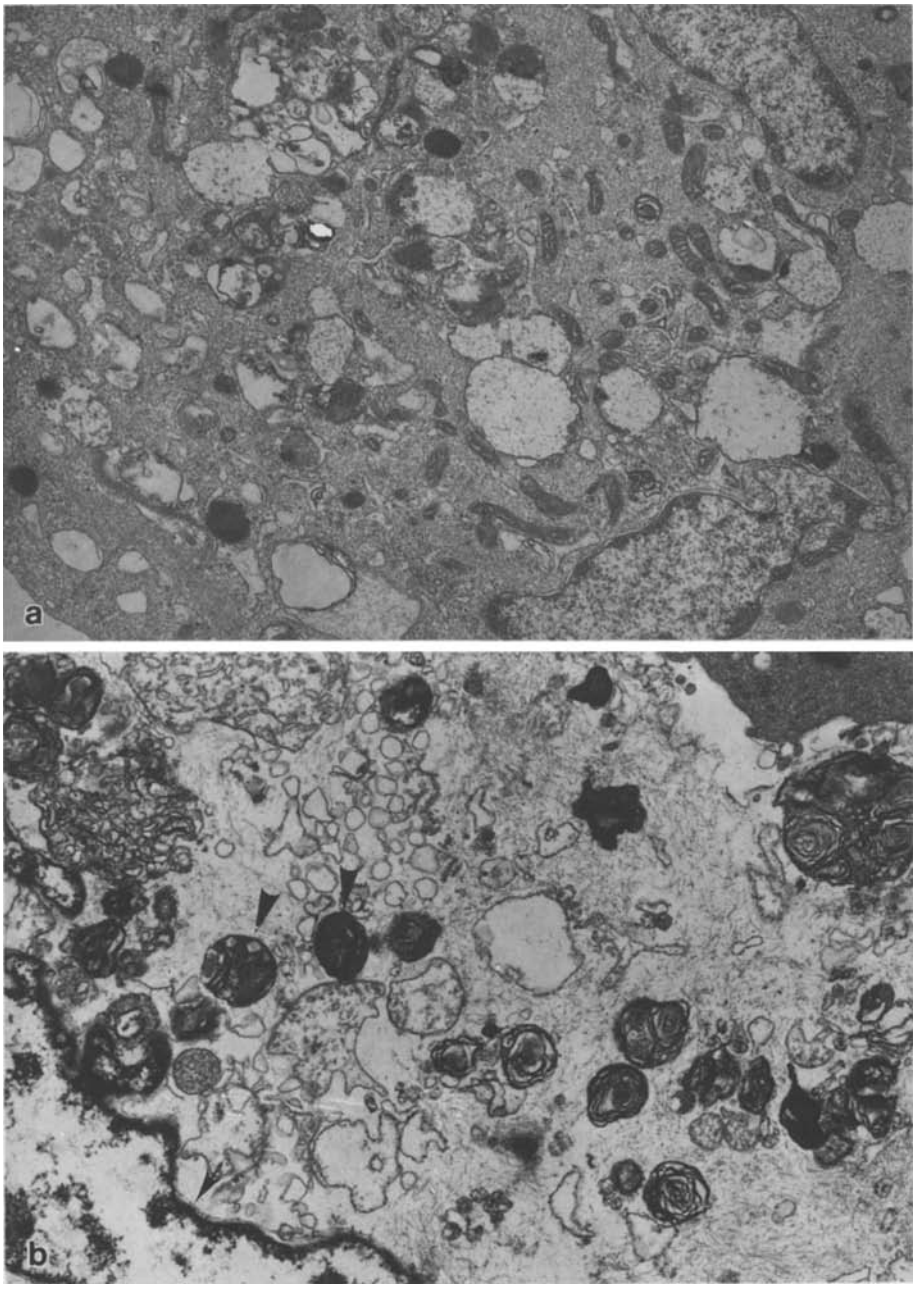

Fig. 6a and b. EM comparison at high magnification (14,625x) after 2,000 SW between a NHEK cells and b RCC cells. The arrowheads depict disintegrating mitochondria and the arrow depicts disintegrated chromatin for the RCC cells

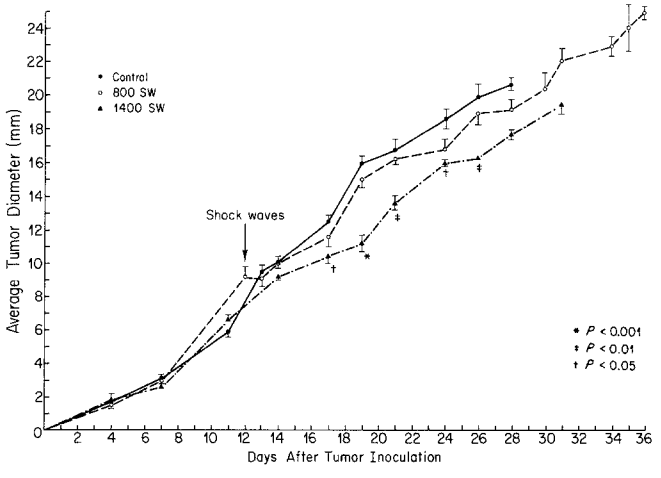

Fig. 7. The effects of • 0, ○ 800 and ▲ 1,400 SW on FANFT bladder tumor growth in C3H/He mice. Shock waves were given at day 12 following tumor inoculation

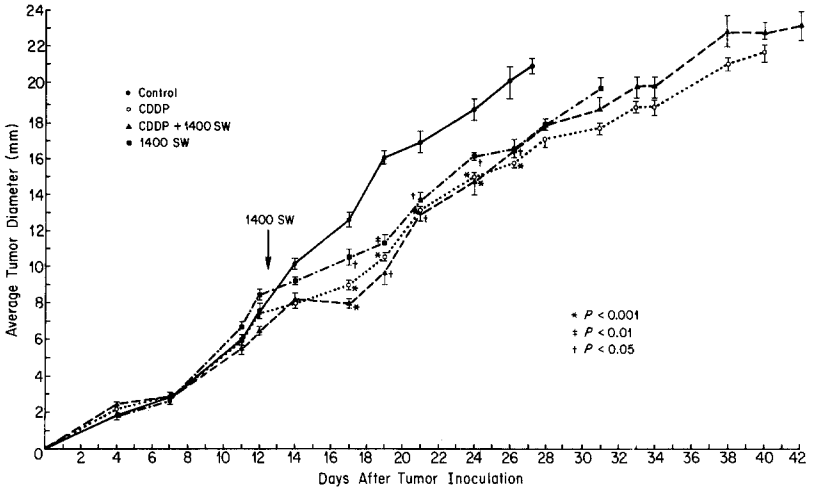

Fig. 8. The effects of cis-diamminedichloroplatinum and 1,400 SW on FANFT bladder tumor growth in C3H/He mice. 1,400 SW was given at day 12. • control, ○ CDDP, ▲ CDDP and 1,400 SW and ■ 1,400 SW

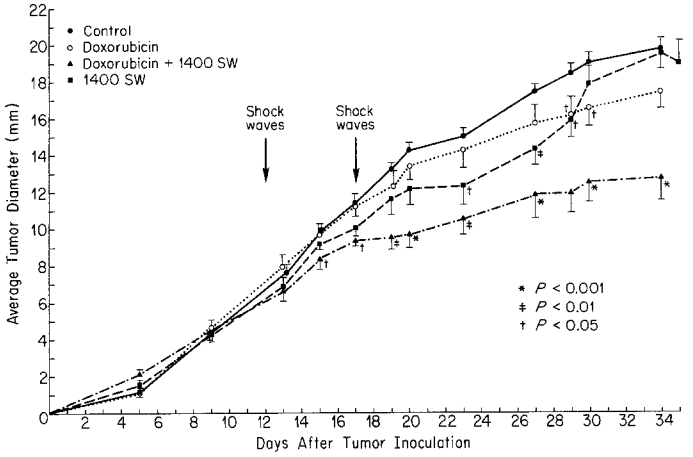

Fig. 9. The effects of doxorubicin and 1,400 SW on FANFT bladder tumor growth in C3H/He mice. 1,400 SW was given on either day 12 or on day 17. • control, ○ doxorubicin, ▲ doxorubicin and 1,400 SW and ■ 1,400 SW

Table 1. Mean tumor diameter for the in vivo experiment which demonstrates the effect of doxorubicin alone and in combination with 1,400 SW on C3H/He mice. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$. Analysis performed between each experimental group and the corresponding control

Days following FANFT tumor cell injection	Mean tumor diameter (mm) control ± S.E. n = 30	Mean tumor diameter (mm) doxorubicin alone n = 20	Mean tumor diameter (mm) doxorubicin and 1,400 SW n = 20	Mean tumor diameter (mm) 1,400 SW alone n = 20
5	1.6 ± 0.2	1.1 ± 0.2	2.2 ± 0.2	1.6 ± 0.2
9	5.4 ± 0.2	4.7 ± 0.4	4.6 ± 0.3	4.3 ± 0.4
13	8.7 ± 0.4	8.0 ± 0.7	6.6 ± 0.5	6.9 ± 0.5
15	10.7 ± 0.4	9.7 ± 0.6	8.4 ± 0.6*	9.2 ± 0.3
17	12.3 ± 0.6	11.3 ± 0.6	9.4 ± 0.3*	10.1 ± 0.5
19	14.2 ± 0.5	12.3 ± 0.9	9.6 ± 0.7**	11.7 ± 0.9
20	14.8 ± 0.7	13.4 ± 0.9	10.2 ± 0.7***	12:2 ± 0.9
23	16.0 ± 0.6	14.3 ± 1.0	10.6 ± 0.9***	12.4 ± 1.1*
27	18.4 ± 0.5	15.8 ± 1.0	11.9 ± 1.3***	14.4 ± 0.9**
29	20.0 ± 0.5	16.2 ± 1.0*	12.0 ± 1.1***	15.9 ± 0.9*
30	20.3 ± 0.6	16.6 ± 1.0*	12.6 ± 1.1***	17.9 ± 1.0
34	21.6 ± 0.7	17.5 ± 0.9	12.8 ± 1.2***	19.6 ± 0.9

Histological Studies. The animals were sacrificed when half of the animals in that group expired. Hematoxylin and eosin light microscopic studies were performed on all control and experimental tumors. No microscopic differences in tumor morphology or necrosis could be discerned between the control and treated groups even with 2,000 SW.

Discussion

The studies of Russo, et al. [4], as well as our experiments have shown that there is a dose-related effect between the number of SW and cell damage. All the parameters of tumor cell injury which we monitored, i.e., cell viability, cell growth, cell attachment and ultrastructural damage, were augmented with increasing levels of shock waves. In the in vivo experiment, 1,400 SW was the lowest level effective in inhibiting tumor growth. This correlates well with the in vitro studies where we begin to see at 1,400 SW significant tumor cell injury as evidenced by the EM studies. At 2,000 SW in the in vitro studies, we saw a significant decrease in RCC viability, cell growth and percent of cell attachment compared to the NHEK cells. The RCC cells appear to be more susceptible to high levels of SW, i.e., 2,000 SW, than are the NHEK cells. Variation in sensitivity to ESW was also seen by Russo, et al. In their experiments the anaplastic prostate cancer cells had a 22% clonogenic survival at 1,500 SW, but the melanoma cells had 0% clonogenic survivals after only 200 SW. One would conclude from these studies that melanoma is exquisitely sensitive to ESW. There appears to be no correlation between the rate at which cells double and the sensitivity to ESW. The anaplastic prostate cancer cells which were moderately sensitive to ESW had an in vitro doubling time of 12 h and melanoma cells which were very sensitive had a doubling time of 24 h. The RCC cell line had a doubling time of 70 h, which was similar to the NHEK cell doubling time of 91 h.

Using flow cytometry determination of DNA, Russo, et al. showed a selective dimunition of cells in the G2 and M phases of the cell cycle. Within 48 h, DNA analysis showed a reversion towards control values. The damage caused by ESW may be specific to these phases of the cell cycle.

One possible explanation for the differential sensitivity of renal carcinoma cells compared to normal embryonic kidney cells is that cancer cells have different cytoskeletons which may make them more susceptible to the mechanical forces associated with shock waves.

An in vivo model was devised to further examine the effects of shock waves on tumor cells; however, the model was not optimal because of the toxic effects of high energy shock waves on mice. In two experiments where the weights of the mice receiving chemotherapy alone or a combination of chemotherapy and 1,400 SW were compared a different effect was seen on body weight. When 1,400 SW was given to mice receiving CDDP there was no change in weight; however, with doxorubicin and 1,400 SW at days 14 and 21 after tumor inoculation, there was a significant decrease (10%) in weight in mice receiving 1,400 SW. The explanation for the weight decrease in the doxorubicin experiment but not in the CDDP experiment is probably secondary to the increase in energy level used in the doxorubicin experiment, 20 kV, compared to 18 kV used in the CDDP experiment. The higher energy level appears more toxic. The mortality rate was also directly related to the number of shock waves and the energy level. At 18 kV and 1,400 SW there were no deaths, but at 20 kV and 1,400 SW there was a 48% mortality rate. At 18 kV and 2,000 SW the mortality rate was 31%.

In the in vivo experiment using CDDP, 1,400 SW and 18 kV, there was no decrease in weight, but a significant decrease in tumor size was still noted with 1,400 SW. Additionally, in the doxorubicin experiment by day 28 the weights were unchanged for mice receiving 1,400 SW and there was still a significant decrease in the 1,400 SW treated tumor size. In conclusion, there appears to be a significant decrease in tumor size in the in vivo experiments which is independent of the effects of shock waves on body weight.

In the vivo experiments the lack of effect of shock waves at day 6 was unexpected and could be explained by the fact that at that time the tumor was not palpable and the shock waves were focused randomly on the thigh and may not have been centered on the tumor as they were once the tumor became palpable.

Clearly the in vivo experiments give preliminary results and further experiments need to be conducted before any solid conclusions can be made. A rat model may better tolerate shock waves. These experiments did confirm the results obtained by Russo et al. [4], i.e., shock waves inhibited in vivo tumor growth.

The exact mechanism of action of ESW is unknown. Four pieces of evidence indicate that this injury may be at a membrane level. First, the ability of cells to attach to the culture plate is effected, possibly indicating some membrane or cell surface changes. Second, electron microscopic study showed significant cellular, mitochondrial and nuclear membrane damage before any changes in chromatin were noted. Third, CDDP which is an alkylating agent had no additive effect with SW in the in vivo experiment; however, doxorubicin, which worked at the cell membrane besides intercalating into DNA, has a synergistic effect with SW. Fourth, and most importantly, was the in vitro cell growth after the first and second passage. If viable cells were taken from each of the treatment groups, the treated cells had identical growth to the control at 12 days after ESW. This last phenomenon indicated that the injury was probably not at the nuclear level, because if the chromatin was sufficiently damaged, one would not expect such complete recovery. It was still possible that the injury was at the chromatin level but that the surviving cells received an insufficient level of SW and the DNA repair mechanisms were adequate to

repair the nucleic acid damage. The effect of 3,000 or 4,000 SW on a similar number of RCC cells is unknown. It is possible that complete chromatin disintegration occurs at these higher levels.

Conclusions

These experiments showed that:

(1) ESW can significantly inhibit in vivo and in vitro tumor growth;

(2) at 2,000 SW there is a significant difference in damage to RCC cells compared to the NHEK cells;

(3) doxorubicin has a synergistic tumor inhibitory effect in vivo with ESW.

Indirect evidence exists which indicates that the cell injury occurs at a membrane level.

ESW could potentially be effective for local tumor control. They have two desirable characteristics: The SW can be focused to 1.5 cm and as the SW travel through tissue to the focus, there is no tissue injury.

The ultimate role of ESW on tumor physiology will depend on further studies using higher levels of SW and combining ESW with other modalities such as other chemotherapies, immunotherapies or possibly radiotherapy.

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Randall F. Randazzo, MD
Cook County Hospital
Division of Urology
1835 W. Harrison St.
Chicago, Illinois 60612
USA