alternative explanations are necessary to accommodate all the available data. A number of studies have shown that p53 moves to the mitochondria in response to stress, suggesting that translocation and binding of p53 to mitochondrial Bcl2 and Bcl-xL may also trigger apoptosis (*10*). In this model the mitochondrial p53 could function as an enabler BH3-only protein to release activators like Bid (see the figure, top). Mitochondrial p53 can also show activator functions such as binding to Bak, which results in the release of Bak from Mcl1 (an anti-apoptotic protein similar to Bcl2 and Bcl-xL) (*11*). Direct activation of Bax by p53 appears to take place in the cytosol (*9*). To address the relative importance of enabler and activator functions of p53, Chipuk *et al.* used a Bcl-xL mutant that binds p53 but not PUMA. Although both wild-type and mutant Bcl-xL inhibited p53-mediated apoptosis, expression of PUMA could only reverse the effect of wild-type Bcl-xL. The implication is therefore that p53 has to be released from Bcl-xL by PUMA to induce apoptosis and that the binding of p53 to Bcl-xL is by itself not a proapoptotic signal. While providing elegant support for the activator function of p53, this observation does not preclude a function for p53 as an enabler and overall it seems likely that coordination of the nuclear, cytoplasmic, and mitochondrial functions of p53 will contribute to the ultimate response to stress.

A number of questions arise out of the Chipuk *et al.* study, including whether p53 requires PUMA, or PUMA requires p53, to induce cell death. The answer to the first question, at least in some cell types, seems to be yes. Deletion of PUMA by genetic knockout or knockdown by RNA interference strategies strongly impairs p53-dependent apoptosis in certain cell systems (*3*). But PUMA may not be unique in this function. A number of other BH3-only proteins, such as Noxa, are transcriptionally activated by p53 and play an essential role in the p53 apoptotic response in some cell types. So it seems likely that under certain conditions, proteins like Noxa might substitute for PUMA. Less clear is whether PUMA might require p53. Initial studies have indicated that PUMA expression is enhanced by withdrawal of serum from cells or by inducing stress in the endoplasmic reticulum, and that this induction of PUMA is p53 independent (*12*, *13*). Furthermore, like p53, the transcription factor E2F1 can activate PUMA expression, and in this case PUMA was shown to contribute to apoptosis without requiring p53 (*14*). Although it is extremely exciting to consider p53 as a functional homolog of an activator BH3-only protein, other proteins, such as Bim and Bid, also display this activity. Because PUMA has an extremely high affinity for the anti-apoptotic Bcl2-like proteins (*15*), it seems reasonable to suppose that in addition to releasing p53, PUMA will also release any bound Bim or Bid. Indeed, the study by Chipuk *et al.* suggests that this is possible, and may go some way to explaining the strong apoptotic activity seen following PUMA expression in some p53-null cells. But regardless of these details, which will undoubtedly be the subject of strong debate and intense research, the p53-PUMA relationship suggested by this model provides a very satisfying explanation to the quandary of why p53 should have evolved both transcriptional and cytoplasmic functions.

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BIOPHYSICS

Harvesting Energy by Improving the Economy of Human Walking

Arthur D. Kuo

Humans are tremendously flexible when converting almost any food into energy, but they are both inflexible and insatiable in their demand for mobile energy in another form: electricity. In the developed world, many people seem more concerned with their cell phone battery life than with their next meal. Given the plentiful and, in many cases, increasing supply of stored onboard energy (that is, fat), could humans not generate the necessary electricity themselves? Hand-operated generators are both inexpensive and effective for short-term use. But a less distracting alternative for the long term might be to generate electricity from walking, given that walking is how humans already expend much of their daily energy. On page 1725 in this issue, Rome *et al.* (*1*) describe a new backpack device that harvests far more energy from locomotion than other methods of obtaining energy from walking, while costing the wearer a surprisingly low amount of metabolic energy. It works by extracting energy through an oscillating sprung mass. Why it works so well is unclear. Perhaps the device reduces the mechanical work required of muscles to walk while carrying a load.

The energy-harvesting backpack succeeds with an approach different from other attempts. More common is to generate electricity from the compression of a shoe (*2*), for example, with piezoelectric crystals. Shoe placement is logical, because it allows the wearer to apply an entire body weight to the device. But displacement must be very small to avoid disrupting gait. The result so far is that low power is generated on average, less than 1 W electrical. An alternative is to place the device in parallel with the limbs, with displacement provided by gross limb motion. Such devices are ungainly and require the human to produce extra force. The approach of the energy-harvesting backpack (see the figure) is entirely different. Conceptually, it resembles the self-winding mechanism of an automatic wristwatch, where power is generated from an oscillating payload, excited inertially through the wearer's motion. Neither force nor displacement is imposed; both arise from the device's dynamics. This idea would seem to have little merit at a larger scale. The watch mechanism is useful because its inertia is small and power requirements are minuscule. A 29-kg wristwatch would hardly be tolerable. Yet the backpack is both comfortable and effective, generating nearly 4 W of electrical power with a similar payload.

The energy-harvesting backpack is also a curiosity because of how well it works. It costs metabolic energy both to walk while carrying a fixed payload (about 590 W) and to perform work on a generator (about 48 W metabolic

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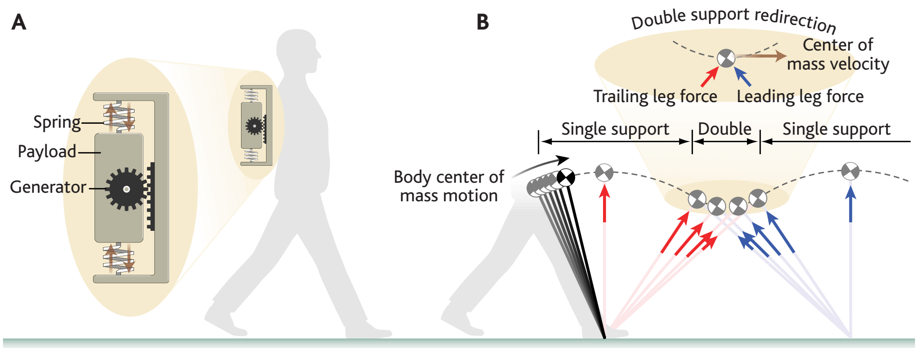
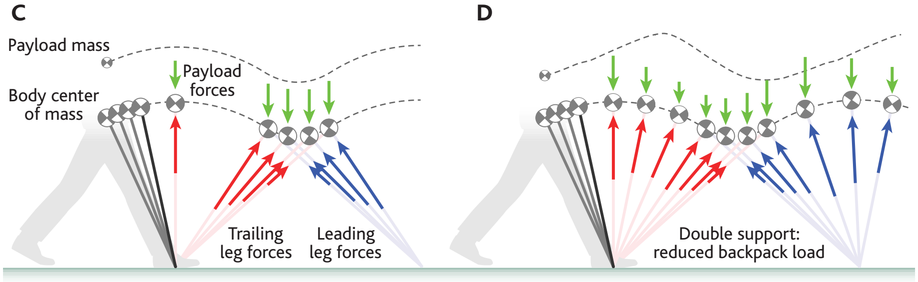


Energy-harvesting backpack

Normal walking



Walking with fixed payload

Walking with oscillating payload

Power walking. Simple models of an energy-harvesting backpack and its relation to human walking. (**A**) Conceptual schematic of backpack, where the payload (the mass to be carried) is supported by springs, and electrical energy is generated when the payload moves up and down. (**B** to **D**) Schematics demonstrate hypothesis for how forces are exerted on the body's center of mass by the legs and backpack. In normal walking (B), the body is supported alternately by one and then two legs (single and double support). The single support leg is relatively straight and the center of mass moves like an inverted pendulum, with no need for energy input. During double support, the legs exert forces to redirect the center of mass along a U-shaped trajectory between successive pendular arcs. The trailing leg performs positive work and the leading leg negative work, with the two nearly canceling each other despite costing metabolic energy. (C) The backpack's payload is fixed to its frame and exerts additional forces on the body center of mass. The inverted pendulum of single support remains energy-conservative, but additional positive and negative work is performed during double support, costing more energy. (D) The payload is unlocked and oscillates vertically. If the motion is properly phased, the backpack load acting on the center of mass may be slightly less than in (C) during double support, requiring less redirection work. The load must then be slightly greater during single support, but if the leg is relatively straight it can support extra load with little muscle force. Some additional muscle work is needed as input to the generator, but this is partially offset by the savings in redirection work. This may explain how the backpack in (D) can generate power more economically than would be expected from (C).

for 12 W mechanical work, due to muscle's efficiency of about 25%). But with the energy-harvesting backpack, subjects expended less than the sum of these two costs, saving nearly 30 W over the expected metabolic rate. It is unlikely that muscle's fundamental ability to perform work had improved. Perhaps the backpack reduces the amount of work needed. But where must work be performed? Walking consists of alternating phases where one leg is kept relatively straight and acts like an inverted pendulum (*3*, *4*). This allows body weight to be supported with relatively little effort, and for the body's center of mass to freely travel along an arc. Some energy must realistically be expended during these pendulum-like phases, but not enough to explain the overall energetic cost of walking, let alone the mysterious advantage of the energy-harvesting backpack.

The explanation may lie in the transition between pendulum-like walking steps, when the body's center of mass is redirected from one pendular arc to the next (*5*, *6*). The center of mass is located near the hip joints and undergoes a small U-shaped displacement during this step-to-step transition, which occurs mainly when both legs contact the ground. Force is exerted by, and directed along, each leg, with the leading leg performing negative work on the center of mass and the trailing leg positive work. The leading leg's force is at such an angle with the direction of center of mass displacement that negative work is unavoidable, if the center of mass is to be redirected to another pendular arc. This negative work is thought to be largely dissipated as an energy loss. An equal magnitude of positive work performed by the trailing leg cancels this loss, as is needed to walk at steady speed. Positive and (to a lesser degree) negative work both cost positive metabolic energy, contributing substantially to the overall cost of normal walking. Now consider that the addition of a fixed payload to the body's mass increases the work required for the step-to-step transition. But a sprung payload, oscillating vertically, exerts a fluctuating load on the body. If the energetic cost of the pendulum-like phase is relatively insensitive to additional load (because the leg need not perform work) and the step-to-step transition is relatively more sensitive (because both legs are performing work), then the sprung payload can prove advantageous by exerting more downward force during the pendulum phase than the step-to-step transition. This might reduce both the work required of step-to-step transitions and the peak forces exerted by the backpack, simultaneously improving energy consumption and comfort. The actual phasing of the prototype device's motion relative to the wearer, not measured here, could indicate whether this hypothesis explains the backpack's advantage.

The energy-harvesting backpack is novel because it generates useful amounts of electrical power while costing less metabolic energy than would be expected. The saving only applies in comparison to a person already walking with a heavy load, but that same person might also be eager to avoid carrying a set of batteries. The backpack also highlights an important aspect of human walking, indicating that muscles perform work that cancels mechanically but costs metabolically. The backpack's sprung payload may reduce this work. Present understanding is incomplete, but there is no obvious reason why the backpack cannot be improved to reduce muscle work requirements still further (*7*). One could then generate electricity while carrying a load more economically and with greater comfort than with a conventional backpack. Future backpackers might be less concerned about both cell phone battery life and their next meal.

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